Textbook of Erectile Dysfunction
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Second Edition

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52 Vanderbilt Avenue
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Printed in the United States of America on acid-free paper
10 9 8 7 6 5 4 3 2 1

Library of Congress Cataloging-in-Publication Data

p. ; cm.
Includes bibliographical references and index.
Carson, Culley C.
Penile Diseases–diagnosis.  4. Penile Diseases–therapy.  WJ 709 T355 2009]
RC889.T49 2009
616.6  ’922–dc22
2008047724

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Composition by Exeter Premedia Services Pvt Ltd, Chennai, India
Printed and bound in the United States of America.
Dedicated to my parents Culley and Dorothy Carson and my wife Mary Jo Carson
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Preface

While the last decade has seen enormous changes in the understanding and treatment of sexual dysfunction and erectile dysfunction, the problem of sexual dysfunction has been described since the ancients. Indeed Greek cup paintings, the Old Testament, Hindus, and ancient Chinese have all described sexual problems. Treatments from surgery, herbs, spices, and potions have all been suggested as remedies. The more modern song describing 'Love Potion Number 9' and the search for 'Spanish Fly' both detail these remedies and their promise of resolution of sexual and erectile dysfunction.

Beginning with Kinsey in 1948 and through Masters and Johnson in the 1960s, the epidemiology and behavioral treatment model has flourished before specific tested medical methods had been developed. Simultaneously, surgeons attempted to recreate the os penis of lower animal forms with surgical procedures beginning with transplanted rib cartilage and proceeding through latex to the currently used silicone elastomer. It has been just three decades since the first functional, safe, and satisfactory penile implant has been introduced.

The true revolution in treatment and patient acceptance, however, began with the marketing of the first phosphodiesterase type 5 inhibitor (PDE-5), sildenafil, in 1998. This revolution was not only scientific and medical, but also societal. Once these PDE-5 inhibitors were available, the international acceptance of the diagnosis and treatment of erectile dysfunction assumed titanic proportions. Subjects confined to the back rooms were suddenly dinner party conversation and the media were rife with reports, debates, and discussion of the treatment of erectile dysfunction and, by extension, sexual dysfunction in both men and women. That landscape continues today and the management of sexual dysfunction has enlarged from strict erectile problems to include premature ejaculation, hypogonadism, and female sexual dysfunction.

This second edition of *The Textbook of Erectile Dysfunction* marks many of those advances. While the first edition included only moderate discussion of the medical treatment of sexual dysfunction and its causes, this edition moves into a higher level of discussion with subjects such as the basic science approach to erection and sexual investigation, a more refined review of the PDE-5 inhibitors including newer agents, and a discussion of central nervous system agents, their advantages, and disadvantages. There is also a complete discussion of the surgical approach to sexual problems including priapism, Peyronie’s disease, and penile implants. The authors of these chapters are chosen from among the world’s experts in this growing field and are each uniquely qualified for reporting on their area of interest. This edition provides a single source for up-to-date information on sexual dysfunction from history to basic science to treatment options.

The editors would like to express their sincere appreciation to all the contributors for their time, efforts, and expertise. Without these efforts this textbook could not have become a reality. We would also like to acknowledge the assistance of the editorial staff who have taken difficult manuscripts and transformed them into complete, understandable, and readable chapters.

*C Carson, R Kirby, I Goldstein, M Wyllie*  
*October 2008*
The history of erectile dysfunction

Sachin Agrawal and William D Dunsmuir

Introduction

Throughout antiquity, erectile function has symbolized virility and manhood. Erections are special to the human male, since in most animals copulation is quick. In the rat, erection and ejaculation are almost simultaneous reflex events. In the dog, copulation lasts around 20 seconds. Even the African ostrich, renowned for his ostentatious courtship displays, completes the act within a minute.1 Throughout nature, strategies have evolved to facilitate penetration. Mammals like the walrus, whale, and orangutan have ossified penile shafts. This os penis, os priapi, or baculum measures up to 3.5 m. However, for some species, survival does not depend on speed. Indeed, the protraction of sex has evolved perhaps solely in humans. Erectile dysfunction has been ever-present, with modern medical practice evolving through observation, experimentation, and refinement of ancient remedies. This chapter examines its impact, tracing its history from antiquity to the present day.

The impact of impotence through the ages

Impotence has influenced society in two ways: through its association with humiliation and through its influence on the validity of marriage. ‘Non-consummation’ claims were frequently used for annulment, these often leveled at the male. Furthermore, humiliation was a powerful form of social control. Many men were ridiculed and destroyed by the public exposure of their impotence. By the 16th century, ecclesiastic trials were widespread. Juries comprising theologians, physicians, and midwives demanded that the accused ‘prove himself’. Galleries delighted at these civic displays of voyeurism, with trial reports distributed in the thousands. So great was public exhalation and fear generated that these courts bestowed tremendous power to the medieval Church (Figure 1.1).2 Only the struggle for power between the Church and State in France (around 1677) led to abolition of these shameful rituals.3 However, the relationship between law, the Church and the medical professions remained unclear. In 1896, the Illinois Supreme Court annulled a marriage on the basis of impotence, with a doctor being called to give evidence.4 This raised an ethical dilemma regarding the professional code of confidence. The doctor eventually testified that excessive masturbation had caused impotence. In this bizarre case, the court ruled that the doctor ‘oversee’ the defendant’s attempts at self-restraint to assess the condition’s curability. The law subsequently changed, introducing the term ‘naturally impotent’ into the statute, making cause immaterial. To this day, impotence remains grounds for annulment.

Since ancient times, the fear of humiliation and concealment has colored the literature. In Satyricon by Petronius, Encolpius was damned to impotence for desecrating the rites of Priapus (the god of fertility). Having been rendered impotent, he was then humiliated by being forced into a public orgy with the priestess Quartilla.5 Exposing the afflicted has forever been of public interest. Take the 19th century English writer and reformer, John Ruskin: his marriage was publicly dissolved on grounds of non-consummation. Ruskin suffered a mental breakdown and retreated into isolation.6 As with so many men, the loss of potency led to the loss of self-worth. Indeed, the presumed impotence and inability of the last Spanish Hapsburg, Don Carlos II (1661–1700), to provide an heir led to the War of Spanish Succession. It is not surprising that so much time and energy has been spent in finding a cure.

Aphrodisiacs and antiquity

Aphrodisiacs derive their name from Aphrodithe, the Greek goddess of love. Since antiquity they have increased sexual drive and pleasure, with many purported to help erectile function. Some may have originated by correcting nutritional deficiencies and improving health. Oysters are rich in zinc, rhinoceros horn contains calcium and amino acids, and chocolate has magnesium and phenylethylamine. Other aphrodisiacs resembled sexual organs, such as the mandrake and the penis or oysters and the ovaries. The majority heightened physical and sexual awareness, indirectly affecting erectile function. Many bizarre remedies exist, including bear’s gall bladder, shark’s fin, powdered lizard, snake’s blood, fermented leeches (mashed into the penis), and the skin and glands of the Bufo toad (which contains bufotenine, a hallucinogenic known as chan su in Chinese medicine).7 Man’s desire has also led to many species of animals being added to the endangered list: powdered rhinoceros horn can cost $27,000 per pound,8 and in Asia dried tiger penis soup costs $350.9
The Spanish fly was probably the most dangerous aphrodisiac; it was used by the Romans and mentioned in the 15th century Arabic text The Perfumed Garden for the Soul’s Delectation. Made from dried beetle, it was actually poisonous, containing as it did cantharadin. It acted by irritating the urogenital tract, causing vasodilatation. Side-effects included infections, scarring, priapism, and even death.

Alcohol is amongst the oldest aphrodisiacs. The Romans believed it increased libido, so much so that they forbade women from drinking it. Absinthe was considered a stimulant, extracted from wormwood; it contained thujol and thujon essential oils and other toxic compounds. It can cause blindness and neurological problems and has been banned in its original form in most of Europe since the early years of the 20th century.

Aphrodisiacs, including alcohol, amphetamines, and marijuana, increase libido and heighten sexual pleasure when used in low doses by reducing anxiety, by neuro-modulation, or by their hallucinogenic effects. Marijuana use was mentioned in Garcia de Orta’s Colloquies on the Simples and Drugs of India. Recently, cocaine has been the aphrodisiac of choice. It reduces norepinephrine reuptake within the brain, prolonging norepinephrine effects in the synapses.

While many remedies have been lost, some, including plant-based aphrodisiacs such as ginseng and yohimbine, remain popular. Many now have scientifically proven mechanisms of action. Yohimbine, an alpha-2-adrenergic receptor antagonist, is the main alkaloid from the bark of the west African tree Pausinystalia yohimbe. These receptors are found in the abdomen, pelvis, and sex organs and are docked with epinephrine. In a normal erection, nerve impulses displace this epinephrine, and yohimbine displaces epinephrine by interfering with this docking. Higher doses cause a rapid heart rate, high blood pressure, anxiety, and over-stimulation. Yohimbine acts as a dual aphrodisiac: it directly affects erections and it heightens arousal. Unfortunately this epinephrine release is a double-edged sword, since higher doses cause a blood shift away from genitalia, making an erection almost impossible. Cocaine and amphetamines also exhibit this feature and can lead to penile shrinkage. Recent reviews suggest yohimbine allows satisfactory erections in 30% of patients versus 14% with placebo. Ambergis, a rare fat-like substance from whales, is cited in Arabic folklore as a powerful aphrodisiac. In rats it increases testosterone and copulatory behavior. Opium poppies have been found to contain papaverine; its mechanism is not fully understood, but it is thought to inhibit phosphodiesterase.

In India, urological ailments were first described around 3000 BC (the Vedic period), peaking during the 9th century BC. Ayurvedic medicine was outlined in the six volumes of the Charaka Samitha. Susrata described systemic surgery in the Susrata Samitha, a text that was translated into Arabic and Latin, later forming part of European medicine as described by Hunter. Both of these works described urological conditions, and Susrata Samitha described several surgical instruments. Ayurveda described erectile dysfunction as treatable throughout all ages. The treatment, vaji karana, involved physical, psychological, and herbal preparations. Susrata Samitha states that this treatment ‘makes a man sexually strong as a horse (vaji) and enables him to cheerfully satisfy the heat and amorous arders of young maidens.’

In ancient Egyptian texts, the Book of the Dead mentions Nymphaea caesarea (the blue lotus) being used as a sexual adjunct and hallucinogenic in religious rituals. It contains apomorphine (a centrally acting dopamine agonist that causes smooth muscle relaxation) and aporphine (which is hydroxylated to apomorphine in the body). In studies, apomorphine hydrochloride is more effective than placebo but clearly less effective than phosphodiesterase type 5 (PDE-5) inhibitors. In the UK apomorphine hydrochloride was discontinued in 2005 for commercial reasons, and it will probably be confined to history. In the Ebers papyrus (prescription 663), weakness of the penis, was called ‘grapo’ and 37 drugs, including honey, were recommended in its treatment.

Antiquity to Enlightenment

In ancient times, agriculture, animal husbandry, and human fertility were linked by religious ritual. The gods of harvest were worshiped with phallic icons, and impotent men turned to the priesthood. Ancient Greeks prayed to Aphrodite, and the Bible describes impotence as divine retribution. In Genesis, God rendered Abimelech impotent for sleeping

Figure 1.1 Medieval Church Court trial. (Reproduced courtesy of Wilma Cluness.)
with Abraham’s wife. Folklore said that God allowed the devil power over the genitals. In medieval times, people believed that if a witch tied a knot in a strip of leather, it empowered the devil to strike a man impotent. We can only guess how many women were persecuted for men’s sexual failings.

Hippocrates (460–370 BC) stated that ‘pneuma’ (air) and ‘vital spirits’ flowing into the penis generated erections and that impotence was caused by imbalances between the humors (blood, phlegm, yellow bile, and black bile) and the elements (earth, air, fire, and water). He believed that sexual excess reduced potency (a theme explored many times since) and that fine cords facilitated erection, rather like a system of ‘pulleys’ connecting the penis and testis. Damage to these fine cords, as occurred with castration, profoundly affected erectile capability. Hippocrates’ teachings pervaded Western medicine until the Renaissance, when increased anatomical and scientific knowledge challenged ‘classical’ models. Leonardo da Vinci (1452–1519) observed that men executed by hanging developed reflex erections. Examining these, he found that they contained blood, not air. In 1677, Reiner de Graaf demonstrated that injecting water into the internal iliac artery generated erections in human cadavers. In 1573, Varilò stated that the ischiocavernous and bulbospongiosus (or bulbocavernosus) muscles impeded venous return by constricting the root of the penis. Eckhard, in 1863, electrically stimulated pelvic nerves (the nervi erigentes) in a dog, inducing tumescence, thus demonstrating a neurovascular component. During the Victorian period (1837–1901), impotence was widely debated (see below), and treatments included quinine, opium, digitalis, and cold salt water sponging as well as more drastic measures such as scarification of the perineum, blood-letting, and the passage of a mercury-covered boogie into the urethra.

The 19th to mid-20th centuries

During the 19th century three schools of thought developed regarding the endocrinology, psychology, and pathology of erectile dysfunction. How these schools evolved, clashed, and fused is explored here.

The endocrine debate

The association between the testis, male behavior, potency, and fertility has probably been recognized since castration started. Neolithic tribes in Asia Minor castrated animals for domestication as early as 4000 BC. In humans, castration probably originated in Babylon in the second millennium BC, to safeguard against adultery. Castration was also practiced for other reasons. The Christian priesthood (ca 3rd century AD) practiced voluntary castration to help self-imposed religious celibacy. Many civilizations regularly castrated slaves to suppress rebellion. Castration was widespread in the eastern Roman Empire, where its critical timing and effects on potency were understood. Boys castrated before puberty were recognizable ‘eunuchoid’, usually with docile personalities. Castrati were also infertile, making ideal guardians for the harems.

However, the notion that castration ensured impotence was far from true. The females of the Roman harems found eunuchs made novel playmates, their sexual prowess often intact with guaranteed contraception (Figure 1.2). Additionally, early Christian choristers, gelded in their youth to ensure their voices were retained, frequently lived sexually active lives. Indeed, Italian literature is replete with stories of castrati and their sexual cavorting. Castration still occurs in India, the Middle East, and China, with its effect on potency now more clearly understood. The Hijaras are an Indian sect of males, convinced (or coerced) into castration. They function as transvestite male prostitutes, many potent, who indulge in sexual paraphilia. Castration for sex crimes was practiced until recently in Europe. Heim reported that 31% of such men remained potent following emasculation and that rapists were more likely to be sexually active than homosexuals or pedophiles. In prostate cancer, 19% of men who undergo surgical or chemical castration will remain potent. Clearly, castration does not always result in impotence.

However, the influence of the testes on sexual behavior is more complex. Even ancient civilizations realized that it influenced potency and libido, with testicles frequently proposed as an impotence cure. Susruta (around 500 BC) advocated the ingestion of testicular tissue to treat impotence. In 1889, Brown-Séquard reported himself ‘rejuvenated and cured of impotence’ following self-injection of aqueous canine testicular extract. Berthold (in 1849) demonstrated a clear androgenic role for the testes. He castrated roosters, causing regression of the comb and wattle, but showed that transplanting testes back into the abdominal cavity prevented this. Defining testicular function caused confusion for the next 100 years. The problem was twofold: crude methodology and man’s desperation led to many erroneous practices. For example, despite Astley Cooper’s sound scientific work (published in 1823) showing that spermatogenesis and testicular function were unaffected by ligation of the vasa, Ancel and Bouin (in 1904) reported different results for the same experiments, claiming that ligation of the vas deferens caused sperm cell atrophy with concomitant Leydig cell

Figure 1.2 Eunuchs were sexually active in the ancient Roman harems. (Reproduced courtesy of Paula Day.)
hyperplasia and suggesting that ligation might increase endogenous male hormone production, benefiting potency and health (Figure 1.3).22

The excitement generated from these findings led many doctors to propose this as an impotence cure. In 1917, the Austrian surgeon and physiologist Professor Steinach (1861–1944) seemingly provided evidence of marked ‘rejuvenation’ in aging rams after vasaligation. Encouraged, he applied this principle to humans, performing numerous procedures on impotent men. Sigmund Freud and William Yeats are thought to be amongst them.33 More alarming were the techniques of Voronoff (1866–1951)34 in France and Lespinasse35 in Chicago (Figure 1.4). They transplanted testicular grafts from apes directly into the human testis or the subcutaneous space (Figure 1.5). In 1918, Dr Leo Stanley, a Californian prison physician, reported improving impotence. He used pressurized syringes to implant strips of testicles from goats, rams, deer, and even dead inmates’ testicles. The testicles were implanted under the abdominal skin of 1000 inmates.36 Despite initial claims, these techniques did not restore the ‘fountain of youth’ or cure impotence. In the 1930s, many clinicians challenged the credibility of the ‘rejuvenists’.37 In 1934, TE Hammond gave one of the most eloquent and ferocious challenges in the British Journal of Urology.38 He reviewed his own series of castrati, men who had lost both testes through accident or tuberculosis. He reported that they were potent and questioned the role of the testicles in erectile physiology. Furthermore, in the early 20th century, castration and vasaligation were used to treat symptoms of prostate enlargement. Naturally, proponents stressed that impotence was an infrequent complication.39,40

The lack of efficacy of both methods, on both prostatic shrinkage and erectile function, were documented long before ‘rejuvenating’ operations became fashionable.41 Clearly, the profession was in a mess.

Scientific studies gradually clarified male genitourinary and reproductive physiology.42 In 1934, WE Lower cleverly demonstrated pituitary gonadotropic control of the testes. By creating a peritoneal anastomosis between two rabbits (coelenteral fusion), he developed an experimental model where he selectively ablated the endocrine system at different levels, conclusively showing that prostatic, erectile, and testicular function were under pituitary control (Figure 1.6).43 Furthermore, in 1931, Butenandt44 succeeded in isolating 15 mg of androsterone from 25,000 liters of policemen’s urine. The synthesis of testosterone from cholesterol followed, performed by Ruzicka45 in 1935. Both men shared the 1939 Nobel Prize for chemistry, spawning an industry around the development and consumption of anabolic androgenic steroids, legally and illegally. This industry’s expansion enabled a greater understanding of how endocrine agents affect erectile and sexual function. Factors included dose, administration and circumstances but, in general, hormone supplementation rarely improves erectile function.21 The overall role of androgens in erectile function is still poorly understood, but in the early 20th century, this only added to the confusion caused by the other two great controversies, the organic and psychogenic debates.

The ‘organic’ versus ‘psychogenic’ debate

During the late 19th and early 20th centuries, proponents of the ‘organic’ and ‘psychogenic’ schools frequently clashed in acrimonious debate. Sigmund Freud founded the discipline of psychoanalysis in the late 19th century. His followers explained impotence in terms of regression of unresolved conflicts. Freud believed that healthy psychological development required the experience of an Oedipus complex during infant sexual development – the erotic attachment of a child to the parent of opposite sex, coinciding with hostility towards the other parent. In later adult life, transference of these feelings to a new sexual partner could result in inner conflict and erectile dysfunction. Many psychiatrists championed psychoanalysis, but treatment was realistically available only to the rich. For most men seeking medical help, the general advice was ‘resensitization’ through long periods of abstinence. Excessive masturbation was cited by many doctors as a cause, creating great anxiety among the youth, who feared they would ‘fail’ in later life.46 In 1927, psychoanalysts that reported repressed sexuality caused over 95% of cases of impotence47 and designed special anti-masturbatory devices (Figure 1.7). In 1934, New York psychiatrists effectively declared ‘open war’ with urologists. In a statement, they urged general practitioners not to refer patients to urologists, and fuelled a bitter debate that raged in the medical literature. Psychiatrists accused urologists of charlatanism, and urologists defended their practice with elaborate descriptions of the pathology they claimed to observe.48
The history of erectile dysfunction

Wolbarst reviewed 300 cases of impotence and claimed that 87% of patients had pathological posterior urethral changes.\(^5\) Max Huhner eloquently summarized its significance in 1936, mounting a sterling defense of urological practice.\(^5\) Huhner described perpetual prostatic ‘irritation’ caused by these urethral swellings, resulting in a constant desire for

Figure 1.4 (a) Voronoff with his monkey. (Reproduced from Chadwick AJ, Mann WN, eds. Hippocratic Writings. London: Penguin, 1987, with permission.) (b) Voronoff performs testicular transplantation from a monkey to man. (c, d) As witnessed by his countenance, an elderly man is markedly rejuvenated following testicular transplantation. (Reproduced from Voronoff S. Rejuvenation by Grafting. London: George Allen and Unwin, 1925, with permission.)

Thomas Curling’s classic publication in 1878 summarized factors thought to be important.\(^4\) He described numerous pathologies, venereal disease in particular, and was probably amongst the first to connect impotence, diabetes, and Peyronnie’s disease. More importantly, he described the cystoscopic appearances of the verumontanum. Many urologists frequently observed inflamed swellings of this posterior urethral structure in patients with erectile failure. Wolbarst reviewed 300 cases of impotence and claimed that 87% of patients had pathological posterior urethral changes.\(^5\)
sexual excess. Men would indulge too frequently in coitus or masturbation and desensitize their erectile centers, causing impotence (Figure 1.8). Common urological treatments included cauterization of the posterior prostatic urethra along with the urethral instillation of cantharides. Psychiatrists including Hammond and urologists like Curling attempted to resensitize erectile centers. They applied faradic electrical current to the penis, prostatic urethra, and spinal cord (Figure 1.9).

Most treatments were disappointing. Psychoanalysis, aphrodisiacs, vasoligation, testicular grafting, forced abstinence, and desensitization (by whatever method) helped but a few people. More practical devices such as suction pumps and penile supports (scaffolds) were introduced in the 20th century (Figure 1.10). Many were patented, and some sold by the thousand. Various surgical techniques were tried. Wooten in 1902, advocated dorsal vein ligation to retard outward penile blood flow. Lilienthal championed this in the 1930s. Further attempts to impede outflow included ischiocavernosal muscle plication by Lowsley and Bray (1936) (Figure 1.11). Despite claims of great success, this last-named procedure has passed into obscurity,
though dorsal vein ligation has drifted in and out of fashion ever since.

**Plastics, prosthetics, pumps and pills**

During the Second World War, many pilots and soldiers lost genitalia through burns and land mines. This saw plastic surgical penile reconstruction develop in the post-war period. Gills and Borgoras were the pioneers, the latter using rib cartilage in 1936 to allow successful micturition and intercourse.\(^5\)
The post-war period was also a time of changing attitudes. Male sexual dysfunction had previously been taboo and free discussion had been repressed. Lesley Hall remarked that even sad heroes of 20th-century literary works – Hemingway’s Jake Barnes in *The Sun Also Rises* and DH Lawrence’s Clifford Chatterley in *Lady Chatterley’s Lover* sustained impotence as unfortunate victims of war. People were uncomfortable identifying with men who had lost their ‘manliness’. The Kinsey Report (1948) highlighted the widespread prevalence of this problem. Attitudes changed slowly, but openness evolved, with more men seeking help.

The 1960s and 1970s heralded the arrival of Masters and Johnson\textsuperscript{61} and Helen Kaplan\textsuperscript{62} and a renaissance of

In 1948 Bergman fashioned a new penis over an autografted rib cartilage (Figure 1.12).\textsuperscript{57} These techniques were extended to treat impotence, but had limited success, owing to eventual cartilage reabsorption. However, they heralded prosthetic implant surgery. In 1964, Loeffler reported the insertion of acrylic rods into the penis to treat impotence.\textsuperscript{58} Beheri independently performed 700 cases in Egypt in 1966.\textsuperscript{59} The original technique described the rods being placed between the tunica and Buck’s fascia, but they were later placed intracavernosally because the initial technique caused pain. Subsequently, numerous and more sophisticated devices have been designed and are commonly used, including newer self-erectable prostheses.

![Figure 1.11](a, b) Ischiocavernosal muscle plication of Lowsley and Bray. (c) Plication is complete. (Reproduced from Zentralbl Chir 1936; 63: 1271–6, with permission.)

![Figure 1.11](c)
‘new sexual therapies’. In 1982, Virag and Brindley introduced the effective intracavernosal agents, papaverine and phentolamine, respectively. In the 1970s, Geddings Osbon created the ErecAid, noting that vacuum devices could cause an erection. The prototype was based on a bicycle pump; currently a number of models are available, providing good results. Prostaglandins and other agents have recently been added to the therapeutic armory. The development of erectile tissue-specific PDE-5 inhibitors has made effective oral agents a reality. Sildenafil citrate, the first PDE-5 inhibitor, was released by Pfizer in 1998; it originated as a drug for heart failure but was observed to cause erections. Newer PDE-5 inhibitors, such as vardenafil and tadalafil, have subsequently been introduced.

The history of erectile dysfunction is ongoing and new chapters are being written, with newer therapies replacing older ones. Increasingly, surgeons, physicians, and psychologists work together in multidisciplinary teams to tackle the multifactorial nature of erectile dysfunction. A great deal has been achieved since the days when men prayed to Aphrodite for deliverance. Many causes have been identified and defined. However, for those affected, the feeling of destruction remains, with solutions still imperfect and limited.

REFERENCES

30. Berthold AA. Transplantation des Hoden [Transplantation of the testicles]. Arch Anat Physiol Wiss Med 1849; 16: 42–6. [In German]
45. Ruzicka L, Wettstein A. Über die Kristallische Herstellung des Testikelhormons, Testeron (Androsten-3-on-17-0l) [The crystalline production of the testicle hormone, testosteron (Androsten-3-on-17-0l)]. Helv Chim Acta 1935; 18: 986–94. [in German]
2 The history of the International Society for Sexual Medicine

Ronald W Lewis and Gorm Wagner

Biennial meetings and structure of the organization

The founding of the International Society for Sexual Medicine can be traced back to a couple of meetings that were held in 1978 and 1980. Dr Adrian Zorgniotti, a urologist with a vision for the future for sexual medicine, became aware of some unique reports on the work of a vascular surgeon, Vaclav Michal (Prague, Czechoslovakia), regarding his success stories on restoration of erectile function in patients having pelvic vascular reconstruction. These surgeries had led him to propose revascularization of the corpora cavernosa directly by anastomosis of the inferior epigastric artery to the corpus tissue.1 Zorgniotti, along with his colleague Dr Giuseppe Rossi, decided to host a meeting at their home institution, Cabrini Medical Center, in New York City, in the fall of 1978. Two other groups were also invited to be a focus of the meeting. Dr Jean François Ginesté (Montpelier, France) was the main presenter for two radiologists who had developed exquisite internal pudendal arteriography studies; and Gorm Wagner (Copenhagen, Denmark) was the presenter for a multidisciplinary group involved in unique diagnostic tests for erectile dysfunction (ED). The interest was so keen after this meeting that it was decided to reassemble after 2 years to see where the science would go. Some of the presentations at this meeting led to the publication of a book, Vascular Impotence: Proceedings of the First International Conference on Corpus Cavernosum Revascularization.2

The second meeting, entitled The Second International Meeting on Corpus Cavernosum Revascularization, took place in October 1980 in Monaco. At this meeting the group of international physicians and scientists focused on alternatives to vascular surgery for ED. A series of articles that focus on the meetings of this society is being prepared by the authors of this book chapter. The first such article, dealing with the details of these first two meetings, called ‘The Beginnings’, will be published in the Journal of Sexual Medicine.3 The breadth of developing science in this field can be found in the subjects discussed at these meetings, which included:

- Measurement of bulbocavernosal latency test
- Early effects of oral atropine, alpha-blockers, and beta-blockers on human penile erection
- Techniques and pitfalls of phallography (which would become cavernosography)
- Anatomic basis of the corpora cavernosa
- Pudendal arteriography
- Microvascular surgery techniques
- The results of treatment of other vascular disease in the pelvis as it relates to postoperative sexual dysfunction
- A very unusual case of a congenital shunt between the corpora cavernosa and the glans of the penis
- Some of the early problems with surgery for arterial vascularization
- A discussion of the drainage system of the penis and how that might be involved with erection
- Complications of the then current vascular surgery.

Zorgniotti and Wagner planned a closed symposium at the meeting in Monaco, inviting key physicians and surgeons involved in cutting-edge research in the field of ED in order to develop agendas for intensified research in this field, possible co-operative research protocols, and areas for future meetings. At the close of the meeting in Monaco, Wagner invited the next meeting to be held in Copenhagen 2 years later.

In their frequent correspondence, Wagner and Zorgniotti continued discussing a name for this developing group. They had truly become the nucleus for these international meetings and at the 1982 meeting in Copenhagen, Denmark, the group decided on a name for the organization: The International Society for Impotence Research (ISIR). The meeting in Copenhagen was still labeled as the Third International Symposium on Corpus Cavernosum Revascularization.

It was at the Copenhagen meeting that the idea of an international biennial meeting was solidified, and it was decided that the 1984 meeting would be held in Paris, France. It was to be hosted by Dr Ronald Virag, a vascular surgeon who had been very active in developing unique techniques for corpus cavernosum revascularization, which he had initially presented at the meeting in Monaco. He was the first to call this biennial meeting the World Meeting on Impotence, and hence his meeting was the first with such a title. He also published a book after the meeting with papers requested and received that represented data presented at the meeting.4
The fifth meeting was held in Prague, Czechoslovakia, in 1986 in honor of Dr Michal. It would be the Fifth Symposium on Corpus Cavernosum Revascularization and the Second World Meeting on Impotence. Injection therapy was highlighted, both at the Paris meeting and at the Prague meeting, with a new agent – prostaglandin E1 – and this received attention at the Prague meeting from Singapore, Japan, and Vienna. Thus, one of the main functions of this society was established – a biennial international meeting at which to share scientific advances in the field. Table 2.1 lists all of the meetings of the Society from 1978.

It is interesting to point out there are only three current members of this society who have attended all of the biennial meetings since 1978 and that each of them has served this society as president: Gorm Wagner (Copenhagen) – president from 1988 to 1992; Ronald Lewis (beginning attendance from New Orleans, Louisiana; then Rochester, Minnesota; now Augusta, Georgia) – president from 1998 to 2000; and Ira Sharlip (San Francisco, California with a brief stint in New Orleans, Louisiana) – president from 2006 to 2008. Table 2.2 lists the presidents, secretaries, and treasurers of the Society.

Highlights of growth of the organization include the following milestones. At the 1992 meeting the first official by-laws of the organization were adopted and the terms of office for the officers were more clearly defined. The office of secretary-treasurer was established at this meeting, originally for a term of 6 years but this was later changed to a 4-year term; Dr Ronald Lewis was elected as the first secretary-treasurer. At the 1994 meeting in Singapore, Dr Robert Krane from Boston was elected president. Dr Krane was one of the major people (along with his young colleague, Irwin Goldstein) responsible for the first meeting of this organization in the USA in 1988 – he worked to develop the ISIR as a parent organization for the developing regional organizations, including the European Society for Impotence Research, founded in 1995 (the future European Society for Sexual and Impotence Research, and then the European Society for Sexual Medicine), the Society for the Study of Impotence, founded in 1994 (to become the Society of Sexual Research of North America and then the Society of Sexual Medicine of North America), the South and Central American Society founded in 1990, which joined ISIR in 1997 (SLAI – Sociedad LatinoAmericana para el Estudio de la Impotencia, later to become the Latin American Society for Sexual Medicine); and he worked towards limited affiliations with the Asian Pacific Society for Impotence Research,

| Table 2.1 Biennial Meetings of the Society |
| Year | Place | Major host |
| 1978 | New York | Adrian Zorgniotti |
| 1980 | Monaco | Adrian Zorgniotti and Gorm Wagner |
| 1982 | Copenhagen | Gorm Wagner |

| Year | Place | Major host |
| 1984 | Paris | Ronald Virag |
| 1986 | Prague | Vaclav Michal |
| 1988 | Boston | Robert Krane and Irwin Goldstein |
| 1990 | Rio de Janeiro | Pedro Puech-Leao and Sydney Glima |
| 1992 | Milan | Eduardo Austoni |
| 1994 | Singapore | Ganesan Adaikan |
| 1996 | San Francisco | Tom Lue |
| 1998 | Amsterdam | Eric Meuleman |
| 2000 | Perth | Carolyn Earle and Bronwyn Stuckey |

| World Conferences of the ISSIR or ISM |
| Year | Place | Major host |
| 2002 | Montreal | Jeremy Heaton |
| 2004 | Buenos Aires | Edgardo Becher |
| 2006 | Cairo | Khhaled Dabees |

| Table 2.2 Officers of the Society |
| Presidents |
| Vaclav Michal | 1978–1986 |
| Adrian Zorgniotti | 1986–1988 |
| Gorm Wagner | 1988–1994 |
| Ronald Lewis | 1998–2000 |
| Sydney Glima | 2000–2002 |
| Jacques Buvat | 2002–2004 |
| Ganesan Adaikan | 2004–2006 |
| Ira Sharlip | 2006–2008 |
| Presidents-elect |
| Jacques Buvat | 2000–2002 |
| Ganesan Adaikan | 2002–2004 |
| Ira Sharlip | 2004–2006 |
| John Dean | 2006–2008 |
| Secretary–treasurers |
| Secretaries |
| Ira Sharlip | 2000–2004 |
| Edgardo Becher | 2004–2008 |
| Treasurer |
| Eric Meuleman | 2000–2006 |
| Luca Incrocci | 2006–2008 |

There was a sharing of profits from the 1994 meeting in Singapore (hosted by Dr Ganesan Adaikan) with ISSIR. At the meeting in 1996 in San Francisco, California (hosted by Tom Lue and his group from the University of California, San Francisco) the first papers on a possible emerging new oral therapy for ED were presented. The group from San Francisco presented to ISSIR a portion of the profits for the specific purpose of sponsoring a new award – the Tanagho Prize (see below).

At the 1998 meeting held in Amsterdam in the Netherlands, a professional organization assisted Dr Eric Meuleman in the arrangements for the meeting. The leaders of the society were so impressed that Status Plus of the Netherlands became the official business office of the society. The Dutch group hosting the 1998 meeting made a donation of $75,000 to the Adrian Zorgnietti Research Fund of the ISSIR.

Dr Lewis, while he was secretary of the organization from 1992 to 1994, suggested that the office of president-elect be established and that the term of the president be limited to a 2-year stint from one biennial meeting to another. The office of secretary was also changed to a 4-year term. The by-laws were changed to reflect these changes, which allowed more of the developing leaders in the field to serve the Society as president. During his term as secretary-treasurer, Jacques Buvat consolidated the bank accounts of the organization under our registered name, as ISSIR, in 1998.

At the meeting in 2000, hosted in Perth, Australia (chaired by Carolyn Earle and Dr Bronwyn Stuckey), the first sessions on female sexual dysfunction were made part of the program. In an effort to solidify this for the future, the name of the organization was changed to the International Society for Sexual and Impotence Research (ISSIR), a bridging name between the old and the final new name.

For the 2002 meeting a professional congress organizer was directly contracted by the ISSIR executive at the suggestion of the local organizer, Dr Jeremy Heaton. As a result, the largest ever contribution to the treasury from a biennial meeting of the ISSIR was made. However, it was decided that our own business office would be more efficient at running future scientific biennial meetings, and thus the 2004 meeting, held in Buenos Aires, Argentina and hosted by Dr Eduardo Becher, was run by Status Plus, our business office in the Netherlands.

During Jacques Buvat’s term as president and Ira Sharlip’s term as secretary, an industrial partnership board was created. The members of the industrial advisory board made significant financial contributions as unrestricted funds to the international society, with the purpose that these funds be distributed among the four regional affiliates that participated in the plan. The European Society of Sexual Medicine decided to remain independent of this plan. In 2001 the ISSIR presented a special symposium during the European Society for Sexual and Impotence Research meeting in Rome, Italy, in order to show solidarity with its affiliated organizations. The title of the symposium was ‘Molecular Mechanisms of Erectile Function’. The speakers were Dr Robert Furchgott, the 1998 Noble Prize recipient, who discovered that the nitric oxide molecule is a messenger for vital functions in the body; Dr Donald Maurice, a key researcher in phosphodiesterase physiology; and Dr Clinton Webb, a prominent smooth muscle physiologist. At the 2003 fourth biennial meeting of the African Society of Sexual and Impotence Research, the meeting was preceded by a full-day ISSIR meeting that covered three topics: education, priapism, and the influence of lifestyle on ED.

At the 2004 meeting in Buenos Aires, the society officially changed its name to the International Society for Sexual Medicine (ISSM), following the lead of two of its affiliates, which had earlier changed their names to the European Society of Sexual Medicine and the Society of Sexual Medicine of North America.

Publications and communications

The second major function of the international society has been the publication of a journal, which began in 1989, just 11 years after the first meeting in New York. The first editors were Drs Gorm Wagner and Bill Furlow (Mayo Clinic, Rochester, Minnesota). They served as co-editors-in-chief from 1989 to 1992. In 1992, Furlow resigned as editor-in-chief and was replaced by Dr Arnold Melman as the new co-editor-in-chief, along with Wagner, until 2002, leaving the journal with an impact factor of 2.7. The journal, entitled at first The International Journal of Impotence Research, started as a four-times-a-year publication, published and owned by Smith–Gordon and Co of London, UK. In 1995, the journal was purchased from that company by Stockton Press. Stockton Press was merged with Nature Publications Group in 2000 and thus the journal came into the ownership of this publisher. In 2003 Irwin Goldstein assumed the office of editor-in-chief of the journal, after the newly appointed Publication Committee headed by John Pryor of London interviewed a strong slate represented by this candidate and three others for the position.

In 2003, it was decided by the leadership of the ISSIR that the journal would be better suited for ownership by the Society. An attempt was made to enquire about sale of the current International Journal of Impotence Research to the ISSIR but Nature Publishing Group was not interested in this offer. The ISSIR then entered into a contract with Blackwell Publishing House to publish a new journal, to be called the Journal of Sexual Medicine. ISSIR would retain ownership of this journal and Blackwell would be the publishing partner. The entire editorial team of the International Journal of Impotence Research moved to the new journal, which became the official journal of the ISSIR and subsequently the ISSM and all of the five regional affiliates. In addition, in 2006 the journal became the official journal of the International Society for the Study of Women’s Sexual Health. It has become the dominant journal in sexual medicine, a monthly journal from 2008; it has a recently announced first impact factor of 4.676. This was impressive from a three-volume start in 2003 to a six-volume journal for the years 2004–2007. In 2008 the journal became a monthly publication. This factor placed the journal fourth in terms of impact factor for all urological and related journals, with the Journal of the American Society of Nephrology, European Urology, and Kidney International as the only such journals ahead of it; the highest impact factor for journals in the andrology category were 2.183 and 2.137. In addition to Irwin
Goldstein, there are nine associate editors: Gloria Buchmann from New Brunswick, New Jersey; Ian Eardley from Leeds, UK; Annamaria Giraldi from Copenhagen, Denmark; Wayne Hestrom from New Orleans, Louisiana; Mario Maggi from Florence, Italy; Chris McMahon from Sydney, Australia; James Pfau from Montreal, Canada; Caroline Pukall from Kingston, Canada; and Ira Sharlip from San Francisco, California.

In August 1998, Jacques Buvat, editor, presented the first issue of the ‘Newsbulletin’ of the ISIR. This was to serve as a newsy communication of the happenings and events of the parent ISIR as well as the affiliates, with information concerning the officers of those organizations and summaries of meetings regarding sexual medicine. As an example of the latter function the first issue contained a take-home message of sexual medicine issues presented at the 93rd Annual Meeting of the American Urological Association in San Diego, California in 1998, prepared by Tom Lue. Luca Incrocci, who joined the editorial committee of the ‘Newsbulletin’ in the May 2000 issue (issue 3), and who assumed the title of associate editor in June 2001, became the new editor-in-chief of the ‘Newsbulletin’ with issue 9, in October 2002. Dr Hussein began to report on summaries of activities of discussions on ISSIR list in the April 2002 issue. Issue 12, in December 2003, marked the Netherlands publication of this communication.

In 2000, the new president of the ISSIR, Dr Sydney Glina, established a website committee. Jacques Buvat was named chairman of this committee. Alexandre Gilbert, the new web administrator, presented the new design of the website in issue 7 of the ‘Newsbulletin’ in December 2001. Dr Gregory Broderick became chairman of the website committee in the fall of 2002. At the biennial meeting of the ISSIR (during which the Society became the ISSM) in Buenos Aires, the website committee and the ‘Newsbulletin’ committee were combined into a single communications committee to be co-chaired by Jacques Buvat and Luca Incrocci.

During Jacques Buvat’s term as president of the ISSM he had the vision to create a standards committee. This committee, under the leadership of Dr Hartmut Porst of Germany and the co-chairman of the standards committee Jacques Buvat, took on the Herculean task of developing a book as a work-product of this committee’s efforts to update current knowledge and present standards in the field of sexual medicine for both sexes. This 28-chapter volume was published in 2006 and represents ‘a focused consonance between clinical problems and contemporary scientific literature’, in the words of Ira Sharlip, the president of the ISSM in the year that the volume was published.

### Scientific awards and research

The ISIR recognized that it should award cutting-edge research with awards at the biennial meetings. Tables 2.3, 2.4, 2.5, and 2.6 list the recipients of these awards over the years. At present the ISSM has four permanent prizes.

- The Jean François Ginéstié Prize of US$2500 was first awarded in 1984. It is funded by the family of Dr Ginéstié, a French pioneer in the field of ED (who performed the first arteriographies of the pudendal arteries). This prize is awarded for the best paper on basic science.

<table>
<thead>
<tr>
<th>Year</th>
<th>Prize Winner</th>
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<tbody>
<tr>
<td>1984</td>
<td>Herbert Newman, USA</td>
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<tr>
<td>1986</td>
<td>P Ganesh Adakian, Singapore</td>
</tr>
<tr>
<td>1988</td>
<td>William D. Steers, USA</td>
</tr>
<tr>
<td>1990</td>
<td>KM Azodzie, USA</td>
</tr>
<tr>
<td>1992</td>
<td>Geng-Long Hsu, Taiwan</td>
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<tr>
<td>1994</td>
<td>Gerald Brock, Canada</td>
</tr>
<tr>
<td>1996</td>
<td>Kwangsung Park, USA</td>
</tr>
<tr>
<td>1998</td>
<td>Gyung-Woo Jung, Korea</td>
</tr>
<tr>
<td>2000</td>
<td>Annamaria Giraldi, Denmark</td>
</tr>
<tr>
<td>2002</td>
<td>Kanhan Chitaley, USA</td>
</tr>
<tr>
<td>2004</td>
<td>John Mulhall, USA</td>
</tr>
<tr>
<td>2006</td>
<td>B Muscicky, USA</td>
</tr>
</tbody>
</table>

- The Zorgniotti–Newman Prize of US$1000 was first awarded in 1988. It is funded by the Zorgniotti Research Fund, itself funded by voluntary donations of ISIR members as well as by a donation from the Dutch organizers of the eight biennial ISIR Meeting, from the profits of this congress. It honors two other famous pioneers in the field of ED, both founders of the ISIR, and is awarded for the best clinical paper.

- The Tanagho Prize of US$1000 was first awarded in 1998. It is funded by the Tanagho Fund, made up of the benefits
of the San Francisco ISIR Meeting (1996). It awarded for the best innovative research.

- The Poster Prize of US$1000 was first awarded in 1990 and is awarded for the best poster.

A female sexual dysfunction prize was announced at the 2002 biennial meeting in Montreal, Canada (Table 2.7).

At the meeting in Amsterdam in 1998, the ISIR presented the first pre-conference symposium. At the same meeting Pfizer Inc made a $50,000 unrestricted educational grant to support young investigators in the field. This was to be divided into five $10,000 grants and to be administered by a panel that reviewed submitted grant applications, chaired by Dr Robert Krane. There were four grant awards announced at the 2000 meeting in Perth, Australia:

- Dr Trinity Bivalacqua, Tulane University, New Orleans, Louisiana – Gene transfer of eNOS and nNOS
- Dr Yutian Dai, Medical College of Georgia, Augusta – Effects of RHO kinase inhibition
- Dr Kwangsun Park, Chonnan Medical University, Kwanjiu, Korea – Effect of hyperglycemia on vaginal function
- Dr John Mulhall, Loyola University, Maywood, Illinois – Analysis of ED as a predictor of coronary arterial disease.

There were six awards in 2001:

- Dr Hunter C Champion, The Johns Hopkins Hospital, Baltimore, Maryland – Role of arginase in aging-associated ED: influence of in vivo gene transfer
- Dr Taben M. Hale, Queen’s University, Kingston, Ontario, Canada – Development of a new therapeutic strategy in sexual dysfunction: pharmacologically targeting vascular remodeling
- Dr Noel N Kim, Boston University School of Medicine, Boston, Massachusetts – Does chronic phosphodiesterase type 5 (PDE-5) inhibition increase PDE-5 activity and attenuate penile erectile function?
- Dr Jonathan Man, Guy’s and St Thomas’ Hospitals, London, UK – Is ED, per se, characterized by generalised increased oxidative stress and endothelial dysfunction?
- Dr Mahadevan Rajasekaran, UCSD Medical Center, San Diego, California – Role of RHO-kinase pathway in hypertension-related male ED?

<table>
<thead>
<tr>
<th>Table 2.6</th>
<th>ISIR Poster Prize winners</th>
</tr>
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<tbody>
<tr>
<td>1990</td>
<td>JA Moreno, USA</td>
</tr>
<tr>
<td>1992</td>
<td>RS Pickard, UK</td>
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<tr>
<td>1994</td>
<td>J Bernabi, France</td>
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<tr>
<td>1996</td>
<td>Hunter Wessels, USA</td>
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<tr>
<td>1998</td>
<td>Yi Tang, France</td>
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<tr>
<td>2000</td>
<td>MA Khan, UK</td>
</tr>
<tr>
<td>2002</td>
<td>Michael Di Santo, USA</td>
</tr>
<tr>
<td>2004</td>
<td>S Úckert, Germany (basic science, female)</td>
</tr>
<tr>
<td></td>
<td>K Park, South Korea (basic science, male)</td>
</tr>
<tr>
<td></td>
<td>R Shabsigh, USA (clinical, female)</td>
</tr>
<tr>
<td></td>
<td>P Teloken, Brazil (clinical, male)</td>
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<tr>
<th>Table 2.7</th>
<th>Female Sexual Dysfunction Prize winners</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>Kathleen Connell, USA</td>
</tr>
<tr>
<td>2004</td>
<td>S Úckert, Germany</td>
</tr>
<tr>
<td>2006</td>
<td>no award</td>
</tr>
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</table>

- Dr Xiaogang Jiang, University Hospital, Copenhagen, Denmark – Uninterrupted 24-hour registration of corpus cavernosum electromyography with a portable recording system.

Another six awards were given in 2002:

- Dr Derek Bochinski, University of California, San Francisco – Comparison of the effect of three combinations in the nerve freezing ED rat model
- Dr Kelvin P Davies, Albert Einstein College of Medicine, Bronx, New York – Changes in global gene expression accompanying ED in diabetics
- Dr Jas Kalsi, Wolfson Institute for Biomedical Research, London, UK – Effect of nitric oxide-independent vasorelaxant agents on cavernosal smooth muscle
- Dr Steven R. King, Baylor College of Medicine, Houston, Texas – Steroidogenic acute regulatory protein’s role in libido
- Dr Guiting Lin, University of California, San Francisco, California – Embryonic stem cells therapy for neurogenic ED
- Dr Ricardo M Munarriz, University School of Medicine, Boston, Massachusetts – Is PDE-5 expression, phosphorylation, or activity regulated by steroid hormones in the penile corpus cavernosum smooth muscle?

The first International Consultation on ED was organized by Dr Saad Khoury and convened in July 1999 in Paris, under the co-sponsorship of the World Health Organization and the Union Internationale Contre le Cancer. This consultation was chaired by A Jardin and co-chaired by G Wagner. Its mission was to develop recommendations for the diagnostic evaluation and management of ED. Recommendations for that meeting were based on a thorough review of the available literature and the subjective opinion of 128 recognized global multidisciplinary experts representing 29 countries and serving on 18 committees. This meeting was co-sponsored by ISIR and the Société Internationale d’Urologie. A book was produced from this effort. This meeting led to the second consultation held in Paris in 2003, again co-sponsored by ISSM and expanded to cover sexual disorders in both men and women. A second book was published in 2004.

**Summary**

The organization that was to become the International Society for Sexual Medicine had its beginnings less than 30 years ago and its first focus was possible revascularization surgery for ED. This organization blossomed at a time when the majority...
of sexual medicine was considered to be in the province of psychological problems. Not long after the first meeting in 1978, other scientific, diagnostic, and therapeutic elements of sexual medicine were placed under more scientific scrutiny. The early founders of the organizations were particularly interested in looking at anatomical and physiological processes that explain normal sexual function as well as pathological dysfunction. This focus led to the decision to have biennial meetings to share cutting-edge findings in the field of sexual medicine. As molecular biology techniques were used to explain other disease processes, the group of scientists who made up this organization easily moved into this more intense scientific evaluation. Not only was the scrutiny afforded to problems of ED, but the members of the organization rapidly realized and expanded into all fields of sexual medicine, so that the organization became the International Society of Sexual Medicine.

The sharing of information on a biennial basis led to the wish to establish a journal to be able to disseminate higher science that was occurring in sexual medicine. However, the field of education was not confined to members of the Society; rather, a new effort was made to educate other healthcare practitioners about sexual medicine; in addition, an effort to help educate the general public in matters of sexual medicine became even a greater focus for the organization.

The Society has continued to be a truly international organization that brings together investigators in various disciplines across the world to define more clearly the biology of sexual medicine. Long-term friendships are forged and scientific enquiry is not only encouraged, but has become the lifeblood of the organization. The attempt of this chapter is to place a historical perspective on how the organization has changed and to introduce some of the key players that have helped nurture and develop it.

REFERENCES

3

Epidemiology of erectile dysfunction

Peter Boyle

Introduction

There is a centuries-old tradition that ‘impotence’ is a consequence of witchcraft or satanic magic.\(^1\) In European culture, the issue is of masculinity with the capacity for a strong erection symbolic of the strong man. Bancroft\(^2\) reviews the history of impotence and the historical literature. The frequency of impotence has not been well investigated until recently and one of the major difficulties is the sensitivity of the information, with respondents tending to give unreliable replies.\(^3\) For example, Marsey et al.\(^4\) investigated the occurrence of impotence in a large cohort of men who had undergone vasectomy, together with an equally large control group. Hidden among questions about many aspects of health and well-being were questions about impotence. These produced incidence estimates of approximately 17 new cases per 100,000 man-years.\(^4\) This is slightly lower than the incidence rate of bladder cancer in the same community and difficult to believe. The epidemiological investigation of impotence has also been held back by the lack of a clear and common definition of the condition.

Impotence is the persistent failure to develop and maintain erections of sufficient rigidity for penetrative sexual intercourse. The disorder is common enough, from all accounts, but there are few reliable data available about the population prevalence. Many patients, and even their doctors, are still very reluctant to discuss such problems and, consequently, a large proportion of both the public and the medical profession are ignorant about available treatment options.\(^5\)

The general terminology used to describe this condition has been moving away from the highly emotive term impotence towards a more widely descriptive term erectile dysfunction (ED). Today it is recognized that the causes of ED are frequently multiple, with psychological, neurological, endocrinological, vascular, traumatic and iatrogenic components described. Very little high-quality epidemiological investigation of ED has been undertaken and completed, so that the relative importance of each of these groups of causes to the overall burden of impotence in the community is unknown at present. There are incomplete indications of a precise role of environmental or lifestyle factors in the development of impotence, although smoking, hypertension, hyperlipidemia, diabetes mellitus and the presence of vascular disease have been proposed as potential risk factors.\(^6\) Research on ED proceeded for many years in parallel among the psychological community and the medical community and it was only after the two groups began serious interaction that true progress was made. Neither group would admit the importance of issues in the other’s domain as a cause of this problem: surgeons pronounced that 80–90% of impotence is caused by physical, not psychological, problems,\(^6\) whereas sex therapists have to come to terms with the fact that many men with erectile dysfunction, possibly as many as 50%, have physical abnormalities that contribute to their erectile problems.\(^1\)

The epidemiology of ED is so poorly understood that to entitle a chapter ‘Epidemiology of erectile dysfunction’, giving the indication that there was some certainty about any statements, is a little presumptuous. In this chapter, the author discusses some of the epidemiological data available, puts it in some perspective and outlines the basic requirements necessary to understand more completely the epidemiological picture.

Erections and the causes of dysfunction

Sexual arousal is a function of great evolutionary antiquity and is often best understood by specialists in research on human nature, such as sociobiologists. Sexual arousal in men is, in some important respects, quite different from sexual arousal in women, particularly with regard to the stimuli and experiences that are optimally exciting.\(^7\) Sexual arousal to erotic stimuli diminishes as initially highly exciting stimuli lose their ability to create arousal with habituation. This has also been shown in laboratory animals, where the male quickly tires of the same partner but thereby rates of intercourse are quickly restored if a fresh partner is found.\(^8\) Farm animals, such as bulls and rams, have a marked preference for novel females: for example, rams introduced to the same partner have a much longer time to ejaculation (around 17 minutes) compared with rams introduced to different partners at the same rate (around 2 minutes).\(^9\) Thus, it could be possible that factors such as habituation could play a part in the development of ED although there are physiological mechanisms as well as psychological mechanisms that must be kept in mind in the potential etiology of erectile dysfunction.
In simple terms, erection of the penis depends on the adequate filling of the paired corpora cavernosa with blood at systolic pressure (or even slightly above).\textsuperscript{2} Erection occurs when the tonically contracted cavernosal and helicine arteries relax, increasing blood flow to the lacunar spaces and resulting in engorgement of the penis. Relaxation of the trabecular smooth muscle of the corpora cavernosa is mediated by acetylcholine, which acts on endothelial cells causing them in turn to release a further non-adrenergic non-cholinergic carrier of the relaxation signal. The strongest suspect for this second carrier is currently nitric oxide, although other candidates, particularly vasoactive intestinal polypeptide, cannot be entirely ruled out at present.\textsuperscript{3}

Thus, the search for etiological factors in erectile dysfunction has certain clues to begin with: factors that interfere with the filling of the corpora cavernosa, with the blood flow to the lacunar spaces, or with the production and regulation of nitric oxide (or other carriers of the relaxation signal) are prime suspects for any etiological investigation.

Erectile dysfunction is not always, however, the failure of some mechanical or biochemical process: sexual function cannot be considered on its own without bearing in mind the concept of sexuality. The human sexual response is a complex, multifaceted phenomenon that is not completely, or nearly, understood by anyone at present. Problems with potency are frequently multi-factorial in origin.

In nervous or anxious men, increased sympathetic tone and raised circulating catecholamine concentrations may interfere with the mechanisms of smooth muscle relaxation underlying erection. Psychogenic impotence is self-perpetuating: each failure increases the associated anxiety levels and frequently can lead to the continual failure to have erections. This is the commonest cause of intermittent erectile dysfunction in young men, although it is usually secondary to organic dysfunction from middle age onwards.\textsuperscript{4}

Free serum testosterone concentrations fall progressively with age, while erectile dysfunction increases in frequency. Falling testosterone levels are associated with a loss of libido and reduced frequency of erections,\textsuperscript{5} although the straightforward restoration of circulating androgen levels often does not restore sexual function. This underlines, once again, the complex nature of male sexual function and the interplay with sexuality.

Although endocrinological impotence frequently is a consequence of poorly understood processes, neurogenic impotence often can have a precise cause attributed. Several neurological disorders can impair erectile function, although it is unusual – but not completely unknown – for impaired erectile function to be the sole manifestation of diseases or disorders of the nervous system. Peripheral neuropathies, most frequently associated with alcoholism or diabetes, are associated with impotence.

Probably the most important causes of erectile dysfunction are impaired blood flow to the penis or excessive leakage from the penis; frequently, both are present. In older men, reduced blood flow into the penis due to atherosclerotic lesions of the internal iliac, pudendal and cavernosal arteries is the most common cause.\textsuperscript{6, 7} With large increases taking place in the aging population,\textsuperscript{8} vascular impotence will take on ever-increasing importance in urological practice.

**Basic epidemiological considerations**

The most useful definition of epidemiology is that it is the scientific study of the distribution and determinants of disease in humans.\textsuperscript{9} From this evolve the two components of descriptive epidemiology – the description of disease incidence, mortality and prevalence by persons, place and time – and analytical epidemiology – the search for determinants of disease risk that may serve to increase prospects for prevention.

Determination of disease frequency, the first step towards geographical and temporal comparisons, relies on a definition (or at least on a working epidemiological definition) of the disease or condition under investigation. ED shares with the other common urological condition of benign prostatic hyperplasia (BPH)\textsuperscript{10} the absence of a unifying definition of which the sensitivity and specificity can be determined. This is a fundamental problem that requires resolution. It should also be a priority to establish a system of classification, after determination of the severity and ‘cause’ of erectile dysfunction.

Many questionnaires have been developed in the hope of achieving this (among other goals),\textsuperscript{11} although many have suffered from being too long and fussy with detail. Recently, two questionnaire-based symptom scales have been developed\textsuperscript{12, 13} that employ modern concepts of psychometric methodology and that attempt to overcome the inherent difficulties experienced with earlier attempts. The brief Sexual Function Index (SFI)\textsuperscript{14} covers the domains of sexual drive, erection, ejaculation, perceptions of problems in each of these areas and overall satisfaction in a total of nine questions. The International Index of Erectile Dysfunction (IIEF)\textsuperscript{15} has been developed and covers in 15 questions the domains of erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction. The similarity of these two instruments, both developed on the basis of detailed statistical analysis, is very reassuring. Time is necessary to observe which comes into the forefront of international usage, although the shorter version of O’Leary and his colleagues\textsuperscript{16} has its attractions, if all other things are equal (i.e. if the questionnaires perform similarly).

A particular problem surrounds the probability of a man declaring his impotence and, to a large extent, this can be influenced by aspects of sexuality. There will be couples who accept the reduction in sexual activity and potency as a natural consequence of aging (and many may, in fact, be pleased and relieved). In similar circumstances, others will be extremely concerned and upset. Such facets of sexuality will have a strong influence on who comes to the doctor or who admits to the interviewer that they have erectile dysfunction. Frequency of self-reports is not to be trusted and consequently will bias any epidemiological study that would investigate the etiology of the phenomenon. Solstad and Hertoft\textsuperscript{17} interviewed 100 men who had previously completed a questionnaire regarding erectile dysfunction: whereas less than 4% of all men who completed the questionnaire (16 of 439) reported erectile dysfunction, among the 100 men from the initial sample who were subsequently interviewed, nearly 40% reported some kind of sexual dysfunction. Interestingly, only 7% found their problems abnormal for their age and only 5% indicated that they would seek treatment for their problems.\textsuperscript{18}
Descriptive epidemiology of erectile dysfunction

The reported frequency of erectile problems in completely unrepresentative samples is very similar. For example, Sanders\textsuperscript{20,21} reports an analysis of responses to two surveys published in *Woman* magazine: 7% of men reported themselves to have erectile problems compared with 8% of women who made the same report. Frank et al.\textsuperscript{22} studied 100 married couples and reported that 7% had difficulty in getting an erection; the same figure (in a study of 58 men) was reported by Nettelbladt and Uddenberg.\textsuperscript{23} Even although the figures are all so similar, this may just reflect the effects of the same major biases that have been outlined above.

Many of these (and similar previous) reports on the frequency of erectile dysfunction are of very limited value, being based on poor epidemiological methodology and likely to be biased in directions that are frequently difficult for the reader to determine; these should be discarded immediately. Even in many recent reports, the methods for obtaining study populations have differed, the definitions of impotence have varied widely from study to study, and stratified information of prevalence by age has frequently been omitted completely or has been unreliable owing to the small numbers of subjects in each of the age classes. These are catastrophic failures from the point of view of comparison of rates. However, some limited data are available regarding the occurrence of ED.

Among 1180 men attending a medical outpatient clinic, Slag et al.\textsuperscript{24} observed that 34% reported impotence to their interviewers. These were attendees at a medical outpatient clinic and may differ from the general population in having over-representation of diabetes, hypertension and other vascular diseases.

Erectile dysfunction is the most common presenting symptom among men attending sexual problem clinics. For example, in Edinburgh, over a 3-year period, over one-half of all men presenting at this clinic reported erectile dysfunction as their main complaint. The next most common complaint was premature ejaculation,\textsuperscript{25} which was reported by 13% of the men. Of these men, over one-half (52%) had some other condition that contributed to their erectile dysfunction: 32% arterial, 21% neurological, 29% urological and 19% diabetes mellitus.\textsuperscript{25} In a similar clinic in Singapore, 72.5% of men attending the Sexual Dysfunction Clinic at Toa Payoh Hospital had erectile dysfunction due to organic causes with the remaining 27.5% of patients having erectile dysfunction due to psychogenic causes.\textsuperscript{26} Of the patients with organic impotence, in 81% of cases this could be attributed to the effects of diabetes and vascular disease.\textsuperscript{27}

In a small study (212 family practice patients) with a young mean age (37 years), 27% of men, on detailed questioning, reported being impotent.\textsuperscript{27} The small sample and the young average age argue strongly against the representativeness of these findings to a community, however.

Morley\textsuperscript{28} determined the prevalence of impotence to be 27% in men of more than 50 years of age undergoing a general health screening. In terms of size of the sample and the mean age of the men, this sample is better than most. However, it is still hindered by the lack of definition of the term impotence and is potentially biased, for reasons associated with the discussion in the previous section.

Diokno and colleagues included questions about sexual activity and its correlates in a clinic examination, whose participants were identified by a household survey of a probability sample of Washtenaw County, Michigan, USA. Men were aged 60 years and over and were questioned with regard to medical, epidemiological and social aspects of aging.\textsuperscript{29} Of married men, 73.8% reported that they were sexually active (whereas the corresponding figure for married women was 55.8%), with levels decreasing with age. Overall, 35.3% of men included in this sample reported that they were impotent.

Feldman and his colleagues conducted the most useful and comprehensive study of the epidemiology of impotence until the present time.\textsuperscript{30} The study sample consisted of respondents to the Massachusetts Male Aging Study (MMAS): this was a cross-sectional, random sample survey of health status and related issues in men aged between 40 and 70 years. The MMAS was conducted between 1987 and 1989 in 11 randomly selected towns in the Boston area of Massachusetts, USA. Of 1709 responders, 1209 men provided complete responses and constitute the sample on which the findings were based. Although the 419 men excluded did not differ from the study sample with respect to all essential variables, a 2/3 non-response rate to sexual questions should be a cause for some hard cynical questioning. A total of 291 men did not respond because they had no sexual partner, and this could bias the prevalence downward. Discriminant analysis was employed to create an impotence scale of nil, minimal, moderate and complete impotence, which was accorded to each individual in the survey.\textsuperscript{30}

Between the fifth and seventh decades, the probability of complete impotence almost tripled, from 5.1% to 15% (Figure 3.1); 60% of men were potent in their fifth decade, whereas only 33% were potent at 70 years.\textsuperscript{30}

Of 1680 men who participated in the (free) Prostate Cancer Awareness Week and who were invited to complete a self-administered questionnaire containing questions on urinary symptoms, impotence, quality of life and age, 1517 answered the questionnaire, a response rate of 90.3%.\textsuperscript{31} A total

![Figure 3.1 Probability of complete or moderate impotence in Massachusetts Male Aging Survey.\textsuperscript{30}](image-url)
of 129 men (7.7%) had not had any erections during the previous 12 months. Of subjects who reported that they had experienced erections during the previous 12 months, 12.4% had had erections on less than one occasion in five when sexually stimulated during the last month. There was a striking association between the frequency of varying degrees of impotence and age.

Sexual function was assessed in the prospective Olmsted County Study of Urinary Symptoms and Health Status Among Men, involving a random sample of men living there. The prevalence of sexual problems and erectile dysfunction increased with age. Comparison of men aged 70–79 years with men aged 40–49 years indicated that older men were more worried about sexual function (46.6% vs 24.9%), had worsened performance compared with a year ago (30.1% vs 10.4%), expressed extreme dissatisfaction with sexual performance (10.7% vs 1.7%), had an absence of sexual drive (25.9% vs 0.6%) and reported complete erectile dysfunction when sexually stimulated (27.4% vs 0.3%). Age did not appear to be an independent determinant of this dissatisfaction; rather, this could be accounted for primarily by the age-related increase in erectile dysfunction, decreased libido and their interaction.

Prior to Jonler et al. and Feldman et al., Kinsey et al. had found impotence to be an age-dependent disorder with a prevalence of 1.9% at 40 years and 25% at age 65. All three studies share the common feature of being based on selected population subgroups. The trends with age, and the high prevalences at older ages, are comfortingly similar, not only to themselves but also compared with other surveys of this area.

Despite the methodological inadequacies in each of these studies, to some degree or another, it is clear that impotence is a very common condition in men and one in which the prevalence is strongly linked to aging. The prevalence probably now exceeds 2% in the fifth decade, rising to 25–30% by the middle of the seventh decade, as estimated by Furlow in 1985. Good data are still required, particularly by ethnic group and at older ages. No data are available for impotence among men aged 75 or over, of whom substantially over one-half may be affected.

Determinants of erectile dysfunction

Until the early 1980s, it was commonly held that psychogenic causes were the etiology in up to 90% of cases of erectile dysfunction. Current thinking favors arterial changes as the key factor in the largest proportion of impotence, with alterations in the flow of blood to and from the penis the single most important cause. Some studies have indicated that there may be evidence of a role for certain cardiovascular risk factors in determining the risk of impotence, including tobacco, hypertension, diabetes mellitus and hyperlipidemia.

Cigarette smoking has been implicated as an independent risk factor for (vascular) impotence. In the MMAS, among subjects with treated heart disease the age-adjusted probability of complete impotence was 56% for current smokers, compared with 21% in current non-smokers. Among treated hypertensives, those who currently smoked cigarettes had an elevated probability of complete impotence (20%), whereas the non-smokers (8.5%) were comparable to the general sample (9.4%). Feldman et al. also found that drug effects were exacerbated by current smoking, which increased the age-adjusted probability of complete impotence in those taking cardiac medication (from 14 to 41%), using antihypertensive medications (from 7.5 to 21%) and using vasodilators (from 21 to 52%). However, in this study an overall effect of current smoking was not noted, with complete impotence present in 11% of smokers and 9.3% of non-smokers. Among current smokers, the probability of impotence demonstrated no dose dependency with current smoking or lifetime cigarette consumption.

Diabetes is widely recognized to be associated with impotence. A review of seven prevalence surveys found rates of erectile dysfunction ranging from 35% to 59% among diabetics. The association with increasing prevalence with age is also found. For example, Figure 3.2 contrasts the prevalence of erectile dysfunction in diabetic and non-diabetic men, and clearly demonstrates the differences between diabetic and non-diabetic men in terms of prevalence of erectile dysfunction as well as the striking association with age in both groups. Similar prevalences have been reported recently and, additionally, erectile dysfunction in diabetic men has been associated with the presence of severe diabetic retinopathy, a history of peripheral neuropathy, amputation, cardiovascular disease, a higher glycosylated hemoglobin, use of antihypertensive drugs and a higher body mass index. It would appear that tighter glycemic control and careful selection of antihypertensive medication could prove beneficial in the avoidance of erectile dysfunction in diabetic patients.

In the MMAS, the age-adjusted probability of complete impotence was three times higher in men who reported having treated diabetes than in those without diabetes. In studies of diabetic patients, there have been consistent findings of high prevalences of impotence, with estimates ranging between one-third and one-half and, occasionally, up to three-quarters. It has been reported that impotence in diabetics increases from 15% at age 30–34 to 55% at age 60 years. It has been reported that impotence occurs at an earlier age in...
men with diabetes than in men in general, both in type I and type II diabetes.\textsuperscript{34,35}\n
Vascular disease is the aspect of diabetes most widely held to be responsible for associated impotence. The association of impotence with vascular disease appears to be quite consistently reported. Impairment in the hemodynamics of erection has been demonstrated in men with a number of vascular diseases: in a group of men aged 31–86 with myocardial infarction, 64% were impotent,\textsuperscript{53} and 57% of men in a study of coronary bypass surgery were found to be impotent.\textsuperscript{54} Similar excesses of impotence have been demonstrated in men with peripheral vascular disease\textsuperscript{35} and cerebrovascular accidents.\textsuperscript{56} It has also been reported that impotence was increased among patients with arthritis,\textsuperscript{57} although Feldman noted that the same association in the MMAS study was confined to smokers.\textsuperscript{50}\n
The effect on sexual function of lifestyle factors related to cardiovascular disorders such as alcohol consumption has been reported to be either slight\textsuperscript{58} or unclear.\textsuperscript{59} There is no consistent evidence suggesting that obesity per se is associated with impotence.\textsuperscript{50,58,59} A high level of total cholesterol or low level of high-density-lipoprotein cholesterol (HDL-C) may result in arteriosclerosis and induce erectile dysfunction by arterial insufficiency. Wei et al.\textsuperscript{60} reported the relation between serum cholesterol and erectile dysfunction among blood samples obtained from the Cooper Clinic in Dallas, Texas, USA. The study included a total of 3250 men aged 26–83 years (mean age reported to be 51 years) without erectile dysfunction at the first visit and who had a further clinic visit between 6 and 48 months following.\textsuperscript{60} Erectile dysfunction was reported by 71 men (2.2%) during this period and every mmol/liter increase in total cholesterol was associated with 1.32 times the risk of erectile dysfunction (95% confidence interval [CI] 1.04, 1.68). Men with an HDL-C measurement over 1.55 mmol/liter (60 mg/dl) had 0.30 times the risk (95% CI 0.09, 1.03). Men with total cholesterol over 6.21 mmol/liter (240 mg/dl) had 1.83 times the risk (95% CI 1.00, 3.37) of that of men with less than 4.65 mmol/liter (180 mg/dl). These differences remained essentially unchanged after adjustment for potential confounding factors (Figure 3.3).\textsuperscript{60}\n
Feldman et al.\textsuperscript{30} reported that the probability of impotence varied inversely with HDL-C. For younger men, aged 40–55 years, the age-adjusted probability of moderate impotence increased from 6.7% to 25% as HDL-C decreased from 90 to 30 mg/dl. In older subjects, aged 56–70 years, the probability of complete impotence increased from near zero to 16% as HDL-C decreased from 90 to 30 mg/dl. No association with total cholesterol was found in this study.\textsuperscript{30}\n
Impotence is often reported following radical prostatectomy, although preservation of the neurovascular bundles helps to reduce the frequency of the condition. Quinlan et al.\textsuperscript{61} reported 600 radical retropubic prostatectomies from the Johns Hopkins Hospital of which 503 men were potent preoperatively.\textsuperscript{61} Three factors were found to be related to the return of sexual function postoperatively, namely age, clinical stage of the tumor and surgical approach – i.e. whether the neurovascular bundles were preserved or excised. In young men, aged less than 50 years, potency was similar in patients who had both neurovascular bundles preserved (90%) and in those who had one neurovascular bundle widely excised (91%). In men over 50 years, sexual function was better in men who had both bundles preserved than in men in whom one neurovascular bundle was widely excised ($p < 0.05$). When the relative risk of impotence was adjusted for age, the risk of postoperative impotence was twofold greater if there was capsular penetration or seminal vesicle invasion, or if one neurovascular bundle was excised ($p < 0.05$). In contrast, the proportion of men who stated that they were impotent following transurethral resection of the prostate (TURP) for BPH (24%) was essentially similar to the preoperative impotence rate (22%).\textsuperscript{62} Previous anecdotal reports of an association between TURP and erectile dysfunction may have arisen because of patients’ confusion in equating retrograde ejaculation with erectile dysfunction.\textsuperscript{63}\n
Of 40 patients with aorto-iliac occlusive disease (AIOD) scheduled for surgery, 31 were given questionnaires and penile dynamic color Doppler ultrasonography.\textsuperscript{64} Five of the 31 who volunteered were found to be potent (16%) and the remaining 26 (84%) were found to have erectile dysfunction. This was found to be entirely arteriogenic in 8% of cases, purely venogenic in 23% of cases and a combination of arteriogenic and venogenic in 53%. Following surgery, 20 patients returned for evaluation and erectile function was found to have improved in seven patients. Of these patients, six (of nine) had undergone endarterectomy and one (of 11) had undergone reconstruction.\textsuperscript{64}\n
The association between impotence and taking medication is still controversial in many instances, as many of these associations have been based on case reports and personal case series. Morley\textsuperscript{23} noted that 16 of the 200 most widely prescribed drugs in the United States were associated with impotence and that 1/4 men in a medical outpatient population were reported to have drug-induced erectile dysfunction.\textsuperscript{24} The frequency of erectile dysfunction was found to be slightly elevated in men receiving finasteride, a 5-alpha-reductase inhibitor used in the treatment of BPH.\textsuperscript{65,66} Erectile

![Figure 3.3](image-url) Relative (and 95% confidence interval) risk of erectile dysfunction by levels of total cholesterol and high-density-lipoprotein (HDL) cholesterol. Data abstracted from reference 60.
dysfunction has been associated with a wide range of anti-hypertensive preparations, including diuretics, sympatholytics, beta-adrenoceptor-blocking agents and vasodilators.67,68 Unfortunately, many of these reports are from studies where the presence of impotence was not ascertained before the trial began and, in most of the studies, it is difficult to separate the effect of the treatment from the effect of the disease. The one exception appears to be doxazosin, an alpha-adrenergic receptor blocker used in the treatment of hypertension and BPH, which was shown in a four-arm study to enhance sexual function.69

Psychological factors directly involved in the development of impotence have been very poorly studied from the etiological point of view. It has not been common practice to include psychological assessments in prospective studies and, in retrospective surveys, it is difficult to avoid the effect similar to confounding by indication, wherein men who become impotent then become depressed and exhibit other psychological traits.

Acknowledgments

This work was conducted within the framework of support from the Associazione Italiana per la Ricerca sul Cancro.

Conclusions and recommendations

With the 20th century has come a wide range of diseases of affluence and aging, including appendicitis, myocardial infarction, osteoporosis and old age. Prior to age 40, impotence is a relatively uncommon disorder but the prevalence rises in such a way that the majority of men over 70 years of age may suffer from erectile dysfunction. Although 100 years ago this was of little consequence in public health terms, today life expectancy approaches 80 years in the most developed countries. Although ED does not kill, it is a major contributor to a reduced quality of life and to the consequent psychological sequelae of many aging men.

The epidemiology of erectile dysfunction is very poorly researched and incompletely understood, although several aspects of the epidemiology are clear, at least in qualitative terms. Most importantly, despite the presence of all possible methodological failings in the available studies, the prevalence of the disease in aging men is very high. The etiology of erectile dysfunction is classified into several major subheadings; whereas psychogenic impotence was held, only 20 years ago, to account for over 80% of cases, today it is widely accepted that the commonest cause, and the explanation for the majority of cases, is the vascular changes commonly found in aging men. In particular, erectile dysfunction appears to be common in diabetic patients and in men with clearly defined, serious vascular disease. A number of risk factors for vascular disease appear to be related to the risk of impotence, including cigarette smoking and serum cholesterol levels, particularly HDL-C. Erectile function also appears to be very sensitive to unrelated drug therapy effects.

Smoking is the largest single source of preventable mortality worldwide today. Smokers have great difficulty in stopping the habit, although it is very tempting to speculate that if it could be demonstrated that smoking cessation reduced the probability of remaining impotent, then men might be more motivated to give up this noxious habit and improve the expected duration as well as the quality of their lives.

There are a number of priorities in epidemiological research on erectile dysfunction. First, it is necessary to develop standard instruments to determine with certain sensitivity and specificity the presence, frequency and nature of erectile dysfunction in men; there have been important developments in this field in the recent past. Subsequently, this should be used to determine variations in the occurrence of erectile dysfunction, be it internationally, temporarily or in special groups of the population; this is now ongoing. There is an urgent need to have a better understanding of the etiology of erectile dysfunction: risk factors need to be identified more clearly so that prevention possibilities can be investigated. In this line, it would be interesting and useful to have urgent information on whether the cessation of cigarette smoking or lowering HDL-C levels could lead to a reduction in the probability of developing impotence. A positive effect of cholesterol-lowering drugs on nocturnal penile tumescence has been observed and, given the association now developing between cardiovascular disease and decreased nocturnal penile tumescence, this could lead to the prioritization of this research line as one important way forward towards prevention. However, this line of etiological and preventive research appears to have stalled and is developing only very slowly at present.

REFERENCES


Anatomy of erectile function

William O Brant, Anthony J Bella, and Tom F Lue

Introduction

The penis is essentially a tripartite structure, with bilateral corpora cavernosa and the midline ventral corpus spongiosum and glans, all three of which are surrounded by loose subcutaneous tissue and skin that can be moved freely over the erect organ (Figure 4.1). The cavernosa function as the main erectile bodies, while the spongiosum contains the urethra. The length of the penis is highly variable, especially in the flaccid state, since it is dependent on the degree of contraction of the cavernosal smooth muscle tissue. There is considerably less variation in length of the fully erect penis, with one study demonstrating a good correspondence between erect length and stretched penile length, as measured from the puboprostatic junction to the meatus. This length was found to be an average of 12.4 cm.

Skin and fascia

Penile skin is continuous with that of the lower abdominal wall and continues over the glans penis; there it folds back on itself and attaches at the coronal sulcus. The folded portion is known as the prepuce.

There are two fascial layers. The more superficial is the dartos fascia, continuous with Scarpa’s fascia of the abdomen. It continues caudally as the dartos fascial layer of the scrotum and Colles’ fascia in the perineum. The deeper fascial layer is Buck’s fascia, which covers the corpora cavernosa and the corpus spongiosum in separate compartments, including coverage of the deep dorsal vein as well as the dorsal neurovascular bundles. Buck’s fascia attaches to the perineal membrane proximally and to the corpora cavernosa distally, where it fuses with the tips of the corpora. The fundiform and suspensory ligaments attach to the pubic symphysis and Buck’s fascia, and allow the erect penis to achieve a horizontal or greater angle.

Tunica albuginea

The corpora are surrounded by tunica albuginea, a strong structure of heterogeneous thickness and anatomy, the purpose of which is to both provide rigidity of the erectile bodies as well as to function in the veno-occlusive mechanism. The tunica albuginea consists of two layers, the outer of which is oriented longitudinally whereas the inner layer consists of circular fibers. The inner layer contains struts that course the cavernosal space and serve to augment the support provided by the intracavernosal septum. The corpus spongiosum lacks both the outer layer as well as the struts.

There is variability in the thickness and strength of the tunica albuginea in various locations. Thickness ranges from approximately 0.8 mm at the five o’clock and seven o’clock positions (just lateral to the corpus spongiosum) to 2.2 mm at the one o’clock and eleven o’clock positions.2

Corpora cavernosa

The paired corpora cavernosa originate separately underneath the ischiopubic rami, then merge as they pass under the pubic arch. The septum between them is incomplete in humans, although complete in some other species. They are supported by several fibrous structures, including the surrounding tunica albuginea, the intracavernous struts radiating from the inner layer of the tunica albuginea, and perineural, periarterial fibrous sheaths. The spongy inner portion of the corpora consists mainly of interconnected sinusoids separated by smooth muscle trabeculae, which are surrounded by collagen and elastic fibers. These sinusoids are larger centrally and smaller towards the periphery. The corpus spongiosum and its distal termination in the glans penis is similar in internal structure to the corpora cavernosa except that the sinusoids are larger, there is a lack of outer layer of the tunica albuginea, and the tunica albuginea is absent in the glans.

Associated musculature

The paired ischiocavernous muscles originate from the ischial tuberosity, cover the proximal corpora, and insert into the inferiomedial surface of the corpora. These muscles are innervated by the perineal branch of the pudendal nerve and allow the corpora cavernosa to obtain much higher intracorporeal pressures than would be possible with arterial pressure alone. The bulbospongiosal muscle originates at the central perineal tendon, covers the urethral bulb and corpus spongiosum, and inserts into the midline. This muscle is innervated by a branch of the perineal nerve and assists in the ejaculation of semen.
Penile vascular anatomy

The main source of blood supply to the penis is usually through the internal pudendal artery, a branch of the internal iliac artery (Figure 4.2). In many instances, however, accessory arteries arise from the external iliac, obturator, vesical, or femoral arteries, and they may occasionally become the dominant or only arterial supply to the corpus cavernosum. Damage to these accessory arteries during radical prostatectomy or cystectomy may result in vasculogenic erectile dysfunction (ED) after surgery. The internal pudendal artery becomes the common penile artery after giving off a branch to the perineum. The three branches of the penile artery are the dorsal, bulbourethral, and cavernous arteries. The cavernous artery is responsible for tumescence of the corpus cavernosum and the dorsal artery for engorgement of the glans penis during erection. The bulbourethral artery supplies the bulb and corpus spongiosum. The cavernous artery enters the corpus cavernosum at the hilum of the penis, where the two crura merge. Distally, the three branches join to form a vascular ring near the glans. Along its course, the cavernous artery gives off many helicine arteries, which supply the trabecular erectile tissue and the sinuoids. These helicine arteries are contracted and tortuous in the flaccid state and become dilated and straight during erection.

The venous drainage from the three corpora originates in tiny venules leading from the peripheral sinuoids immediately beneath the tunica albuginea (see Figure 4.2). These venules travel in the trabeculae between the tunica and the peripheral sinuoids to form the subtunical venular plexus before exiting as the emissary veins. Outside the tunica albuginea, the venous drainage is as follows:

1. The skin and subcutaneous tissue drain through multiple superficial veins that run subcutaneously and unite near the root of the penis to form a single (or paired) superficial dorsal vein, which in turn drains into the saphenous veins. Occasionally, the superficial dorsal vein may also drain a portion of the corpora cavernosa.
2. In the pendulous penis, emissary veins from the corpus cavernosum and spongiosum drain dorsally to the deep dorsal vein, laterally to the circumflex vein, and ventrally to the periurethral vein. Beginning at the coronal sulcus, the prominent deep dorsal vein is the main venous drainage of the glans penis, corpus spongiosum, and distal two-thirds of the corpora cavernosa. Usually, a single vein, but sometimes more than one deep dorsal vein, runs upward behind the symphysis pubis to join the periprostatic venous plexus.

3. Emissary veins from the infrapubic penis drain the proximal corpora cavernosa and join to form cavernous and crural veins. These veins join the periurethral veins from the urethral bulb to form the internal pudendal veins.

Lymphatics

Lymphatics of the prepuce and penile shaft converge dorsally, and then drain into both right- and left-sided superficial inguinal lymph nodes via channels alongside superficial external pudendal vessels. Lymphatics of the glans and penile urethra pass deep to Buck’s fascia and drain into both superficial and deep inguinal nodes.

Innervation

The penis is supplied by both somatic and autonomic nerves. The somatic dorsal nerves provide sensory innervation (as well as provide some degree of autonomic function) for the penile skin and glans, and approximately follow the course of the dorsal penile arteries, eventually becoming the pudendal nerve (after joining with other nerves) and entering the spinal cord via S2–S4 nerve roots. Sympathetic autonomic fibers derive from the hypogastric plexus and join parasympathetic autonomic fibers from S2–S4 in the pelvic plexus. Cavernous nerves represent the penile branches of the pelvic plexus that ramify once they have pierced the corporal bodies, and thus contain both sympathetic and parasympathetic fibers.
Figure 4.2 Arterial and venous anatomy of the penis. (a) penile arterial supply; (b) penile venous drainage; (c) cross-sectional penile and related pelvic venous drainage. With permission from Mulcahy JJ, ed. Male Sexual Function, 2nd edn. New Jersey: Humana, 2006.

REFERENCES

Microscopic anatomy of erectile function

Anthony J Bella, William O Brant, and Tom F Lue

Introduction

Penile erection is dependent upon successful integration of gross and microscopic aspects of neurovascular function, culminating in the hemodynamic changes of turgescence. Recent progress in the understanding of physiologic mechanisms responsible for erectile function has been accompanied by the identification and characterization of key penile ultrastructural components that are able to respond to various stimuli or provide a physical framework for increased blood flow to the corpora cavernosa and veno-occlusive trapping that restricts outflow. In this chapter, the microscopic anatomy of the tunical fibroelastic skeleton of the penis, corpora cavernosa (supportive and smooth muscle components), and penile innervation and blood supply are reviewed in the context of the erectile process.

Tunica albuginea

The primary function of the tunica albuginea is to afford rigidity, flexibility, and tissue strength to the penis. It is a bilayered covering of the corpora cavernosa with multiple sublayers (Figure 5.1). The inner-layer bundles of the corpora cavernosa are circular, and serve to support and contain the cavernous tissue. Furthermore, intracavernous pillars radiate from the inner layer into the corpora, acting as struts to augment the penile septum and provide support to the erectile tissues. The outer longitudinally oriented layer is composed of connective tissue bundles that extend from the glans penis to the proximal crura, inserting on the inferior pubic rami.2

The tunica itself is composed of elastic fibers that form an irregular, latticed network on which the collagen fibers rest (Figure 5.2). This ultrastructural arrangement provides strength and allows the tissue to return to its baseline configuration after the corporal expansion during erection. Key to this function is the composition and distribution of component fibers; the tunica albuginea is primarily composed of type I, but also of type III, fibrillar collagen in organized arrays, throughout which are interspersed elastin fibers.3 Both fiber types are essential for normal function; the steel-like tensile strength of collagen is unyielding and resists uncontrolled deformity at high pressure, while elastin content allows for tunical expansion because these fibers are able to stretch to approximately 150% of ‘resting’ length.4 Elastin content is also a key determinant of stretched penile length.

The presence or absence of both tunical layers, the thickness of the tunica itself and of the intracavernous pillars varies throughout the course of the penis, as does the histological composition, reflecting the relationship between anatomical ‘design’ and function. The strength and thickness of this layer correlates with location, with the thinnest portion noted to be between the 5 o’clock and 7 o’clock positions.5 This coincides with the absence of the outer longitudinal layer at the ventral groove over the urethra; extrusion of penile prosthesis is most common at this location.6 As the crura diverge proximally, circular fibers provide sole support. A higher elastin-to-collagen ratio, as well as the absence of the outer layer and struts, for the tunica overlying the corpus spongiosum ensures a low-pressure structure during erection.7

The average thickness of the tunica is also seen to relate to the stress forces applied to this structure prior to penetration (i.e., during rigid erection). The 0.8 ± 0.1mm thickness between the 6 o’clock and 7 o’clock positions has associated forces of 1.6 ± 0.2 x 10^6 Newtons (N/m²), there is 1.2 ± 0.2mm thickness at the 9 o’clock position, with 3.0 ± 0.3 x 10^6 N/m², and 2.2 ± 0.4 mm thickness at the 11 o’clock position, with 4.5 ± 0.5 x 10^6 N/m² (mirror-image measures are nearly identical).5

In addition to providing a supportive framework to the paired corpora, the tunica albuginea is essential to venous trapping, and pathophysiological changes such as those seen with Peyronie’s disease may compromise this function and lead to venous leak. The emissary veins, as described in Chapter 4, travel between the inner and outer layers of the tunica for short distances, and often pierce the outer bundles in an oblique manner (Figure 5.3).8 The outer longitudinal layer serves as a backboard, resulting in compression of the emissary veins during penile engorgement and limiting the amount of penile blood that is able to drain away from the corpora (Figures 5.4 and 5.5). The end-result is maintenance of an erect penis. Inadequate venous occlusion may result in erectile dysfunction (ED) via the following mechanisms:9

- degenerative tunical changes secondary to Peyronie’s disease, aging, or diabetes, or secondary to traumatic injury impairing subtunical and emissary vein compression;
- alteration in the fibroelastic components of the cavernous smooth muscle, trabeculae, or endothelium;
Corpora cavernosa ultrastructure, the corpus spongiosum and the glans penis

The spongy corpora cavernosa are paired cylinders contained within the supportive envelope of the tunica albuginea; located on the dorsal aspect of the penis, the proximal ends (crura) originate at the undersurface of the puboischial rami as two separate structures and merge under the pubic arch, continuing as a unit to the glans. Support for the corpora is provided by a fibrous skeleton that includes the tunica albuginea, the intracavernous pillars, the intracavernous fibrous network, and the periartreral and perineal fibrous sheath. The midline corporal septum is incomplete, allowing blood to flow from one side to the other.

As with the tunica, cavernosal design reflects a functional need for rigidity, strength, and flexibility. It has been suggested that the intracavernous fibrous framework adds strength to the tunica albuginea. Within the tunica are the interconnected sinusoids separated by smooth muscle trabeculae and surrounded by collagen (predominantly types I and IV), elastin, fibroblasts, and loose areolar tissue. Smooth muscle predominates, accounting for 45% of corporal volume. Alterations of the cytoskeleton either for tissue type components or for relative quantities may be responsible for changes in penile morphology in flaccid and erect states. For example, loss of compliance of the penile sinusoids has been observed as a by-product of aging, and is associated with increased deposition of collagen; hypercholesterolemia-induced dysregulation of collagen may also cause loss of compliance.

Inherent differences for the arterial system ensure that occlusion by the tunica albuginea does not occur during tumescence; the cavernous artery and branches of the dorsal artery traverse the outer layer in a more direct (perpendicular) manner and are instead surrounded by a periartreral fibrous sheath, limiting occlusive ability.

• inadequate cavernous smooth muscle relaxation;
• acquired venous shunts; or
• congenital anomalous large venous channels.

Terminal branches of the cavernous nerves and helicine arteries are intimately associated with corporal smooth muscle; sinusoids are larger in the center and become progressively smaller towards the periphery. Blood slowly diffuses from the central to the peripheral sinusoids in the flaccid state, and the blood gas levels are similar to those of venous blood. During
erection, the oxygen tension approximates that of arterial blood due to the rapid entry of arterial blood to the central and peripheral sinusoids.

Corporal geometry is a key characteristic that allows erections to occur. Midline septal fibers stretch tautly between the dorsal and ventral corporal aspects, creating a functional ‘I-beam’, resulting in anteroposterior rigidity. Relative indispensability of the paired lateral columns adds to stability during erection, while intrasinusoidal pressures within the corpora distend the tunica albuginea to its maximal capacity. The tunica itself resists out-of-column deformities.

The structure of the corpus spongiosum is similar to that of the corpora except that sinusoids are larger and the outer layer of the tunica is absent. Intraspongiosal pressures reach only one-half to one-third of those of the cavernosa, owing to the less constraining tunical layer, resulting in lesser venous occlusion. The glans itself has no tunical covering, but is able to engorge, owing to the presence of continued arterial inflow and venous outflow during erection (a functional arteriovenous fistula). Partial compression of the deep dorsal and circumflex veins between Buck’s fascia and the engorged corpora cavernosa also contribute to glanular tumescence. During the rigid erection phase, spongiosal and penile veins are externally compressed by the ischiocavernosus and bulbocavernosus muscles, further increasing engorgement and pressure in the glans and spongiosum.
Cavernous smooth muscle

In the flaccid state, cavernous (or corporal) smooth muscle is tonically contracted with a partial pressure of oxygen measuring approximately 35 mmHg. Blood flow to the penis is approximately 5 ml per minute. With sexual stimulation and the release of neurotransmitters from the cavernous nerve terminals (see Chapter 11) smooth muscle relaxation occurs, and the end-result is an erect penis. Modulation of the cavernous smooth muscle tone is a complex process regulated by a myriad of intracellular events and extracellular signals, and therefore it is not surprising that the ultrastructure reflects these physiologic functions.

Cavernous smooth muscle cells are composed of thin, intermediate, and thick filaments, which are primarily composed of, respectively, actin, desmin or vimentin, and myosin. In humans, two types of electrical activity have been reported for the corpus cavernosum: spontaneous and activity-induced. Further, DiSanto and associates have reported overall composition to be in between that of aortic (tonic) and bladder smooth muscle (phasic). Smooth muscle contraction and relaxation is primarily regulated by sarcoplasmic free calcium. Each of the filament types has a specific role, but the primary mechanism is the interaction between actin and myosin. Contractile tone is conferred by cross-bridges linking regulatory myosin light chain globular heads and actin; tone is maintained with minimal expenditure of energy. Relaxation occurs as cytosolic calcium is lowered.

Smooth muscle fibers damaged by vasculogenic or neurogenic causes of impotence demonstrate similar ultrastructural changes, suggesting a variety of pathological mechanisms with common end-points. Patients undergoing implantation of a penile prosthesis for ED of varying etiologies have been shown to have a decreased number of smooth muscle cells and sinusoidal endothelial changes. The decreased oxygen tension of arteriogenic ED may diminish trabecular smooth muscle content, leading to venous leakage. Hypercholesterolemic rabbits demonstrate early atherosclerotic changes and significant smooth muscle degeneration with loss of cell-to-cell contact. Diabetes may compromise contractility, reduce cavernous smooth muscle content, thicken the basal lamina, increase collagen, and cause the loss of endothelial cells. Cavernous nerve injury at the time of radical prostatectomy may also decrease levels of cavernous smooth muscle while increasing collagen content, compromising the erectile process.

Functional neuroanatomy

Penile innervation is both autonomic (sympathetic and parasympathetic) and somatic (sensory and motor). The cavernous nerves are the primary influence on the neurovascular events during erection and detumescence; they originate from neurons in the spinal cord and peripheral ganglia, and they consist of sympathetic and parasympathetic fibers (Figure 5.6). Somatic nerves fulfill sensory roles and contract the bulbocavernous and ischiocavernous musculature.

Parasympathetic fibers originate from the second, third, and fourth sacral vertebral segments (S2, S3, and S4) of the spinal cord; S3 is the primary source of erectogenic fibers. The cavernous nerves project from the pelvic plexus, leaving the pelvis between the transverse perineal muscles and membranous urethra. Cadaveric dissection has identified medial and lateral branches, which accompany the urethra and pierce the urogenital diaphragm 4 mm and 7 mm laterally to the sphincter, respectively, as well as multiple communications between the cavernous and dorsal nerves. Since cavernous nerve damage during extirpative surgeries for prostate, bladder, and rectal cancer commonly causes neurogenic ED, it is essential to understand their anatomic course. Preservation and minimal disruption of these nerves is paramount, because they represent the final pathway for vasodilatory and vasoconstrictive input to the cavernous smooth muscle; cavernous nerve injury may also occur secondary to pelvic fracture, with ED the end-result of direct nerve trauma, vascular insufficiency, or a combination of both. The cavernous nerve itself divides into a lesser branch (supplying the corpus spongiosum erectile tissue and penile urethra) and a major branch (enabling penile erection). The major branch courses along the prostatic-vesicular artery and veins as part of the neurovascular bundle of the prostate.

- After passing the tip of the seminal vesicle, the cavernous nerve continues along the posterolateral aspect of the prostate at the five o’clock and seven o’clock positions within the endopelvic fascia.
- At the level of the prostatic apex and membranous urethra, the nerves are located at the three o’clock and nine o’clock positions.
- Distally, some fibers penetrate the tunica albuginea of the corpus spongiosum while the remaining fibers proceed more anteriorly at the eleven o’clock and one o’clock positions. These enter the penile crura along with terminal branches of the pudendal artery and exiting cavernous veins.
Sympathetic preganglionic cavernous nerve fibers are primarily responsible for detumescence; these fibers arise from preganglionic neurons in intermediolateral gray matter from the eleventh thoracic (T11) to the second lumbar (L2) spinal cord segments. Variability in cavernous nerve composition (i.e. in the ratio of parasymathetic to sympathetic fibers), as well as in sympathetic fiber origin (from as high as the ninth thoracic cord segment to as low as the fourth lumbar cord segment), has been described.25 These preganglionic fibers most commonly arise from the tenth thoracic to the second lumbar segments, passing to the paravertebral sympathetic chain ganglia where synaptic connections with ganglion cells are formed. Postganglionic fibers originating in the sacral and caudal lumbar ganglia proceed to the urogenital tract via the cavernous nerves as well as via the pelvic and pudendal nerves. A second pathway for sympathetic preganglionic fibers occurs without lumbar sympathetic contacts; fibers leave the chain ganglia and pass along the lumbar splanchic nerves to prevertebral ganglia in the superior hypogastric plexus (overlying the great vessels at the third lumbar to first sacral vertebrae).3 The superior hypogastric plexus (or presacral nerve) divides into the left and right hypogastric nerves, descending to the inferior hypogastric (or pelvic) plexus. In addition to their role in the erectile process, sympathetic fibers from T11–L2 are also responsible for contraction of internal accessory organs (prostate smooth muscle, seminal vesicle, and bulbourethral gland), ducts (ejaculatory ducts, vasa deferentia, ductus epididymis, ductuli efferentes), closure of the internal urethral sphincter, and ejaculatory emission.2,3,26

Sensory (somatic) function of the glans is unique, in that 80–90% of afferent glans terminals are unmyelinated C or myelinated A-δ fiber-free nerve endings.26 Sensory pathways also originate at receptors found within the penile skin, urethra and corpus cavernosum, with nerve fibers from these receptors converging to form bundles of the dorsal nerve of the penis. The dorsal nerve joins other nerves to become the internal pudendal nerve, entering the spinal cord at the dorsal roots of S2–S4 to terminate in the central gray region of the lumbar sacral segment.2 Spinothalamic and spinoreticular pathways to the thalamus and sensory cortex convey messages of pain, temperature, and touch via the dorsal and pudendal nerves. Afferent input from the skin and glans is also the mechanism responsible for reflexogenic erections. It is important to note that the dorsal nerve of the penis is not purely somatic, but also contains nerve bundles demonstrating nitric oxide synthase, which is indicative of autonomic function, therefore providing evidence for a dual role (erectile and ejaculatory function).27

The center of somatomotor penile innervation is Onuf’s nucleus in S2–S4. The motor pathway to the penis traverses the sacral nerves to the pudendal nerve, innervating the bulbocavernous muscle (rhythmic contraction of ejaculation) and ischiocavernous muscle (contraction results in the rigid erection phase) via the perineal branch. The pudendal nerve leaves the pelvis via the greater sciatic foramen on the medial aspect of the internal pudendal artery; it continues as the dorsal nerve of the penis along the dorsal artery, terminating at the glans.28

**Intercellular communication**

Histological studies of the cavernosal tissues have demonstrated that autonomic innervation consists of widely spaced nerve fibers. However, the process of penile erection and detumescence requires a co-ordinating mechanism among the cavernous smooth muscle fibers that allows synchronized relaxation and contraction; electromyography confirms that activity in the cavernous tissue of patients with normal erectile function is synchronous.29,30

Transport channels termed ‘gap junctions’ are present in the membranes of adjacent cavernous smooth muscle cells, allowing exchange of ions such as calcium and second messenger molecules.31 Electron microscopy demonstrates prominent gap junctions, which are formed by a hemichannel hexamer of connexin proteins, creating pore-like aqueous intercellular channels.24 The major component of gap junctions is connexin-43, a membrane-sparing protein of less than 0.25 µm that has been identified between smooth muscle cells of human corpus cavernosum and that facilitates the transmission of electrical or chemical signals.32 Cell-to-cell myocyte communication does not occur via individualized innervation, rather via gap junction links that allow synchronized smooth muscle tone. These connections have been shown to modulate nitric-oxide–induced cavernous smooth muscle relaxation, as well as alpha-1-adrenergic- and endothelin-1–induced contractility. Although their pathophysiological impact is not fully elucidated, connexin-43 expression in cavernous tissues excised from men with organic erectile dysfunction demonstrates significant heterogeneity.3 For example, in men with severe arterial disease, a loss or reduction of membrane contact has been demonstrated as the presence of collagen fibers between cellular membranes alters the co-ordinated smooth muscle response to erectile stimulus.33

**Arterial microanatomy of the penis**

The majority of the arterial supply to the erectile tissue is via the cavernosal artery, which itself is a branch of the internal pudendal artery (the terminal branch of the hypogastric artery) (Figure 5.7). The cavernosal artery extends through the cavernosal bodies after entering at the inferomedial aspect of the hilum of the penis where the crura merge, piercing the tunica. At the base of the penis the cavernosal arteries are close to the septum, whereas distally they are centrally located in each cavernosal body. Two types of branches occur: outer capillaries, which provide nutrition during flaccidity, supplying the nerve fibers and smooth muscle; and multiple helicine branches, which supply the erectile tissue, opening directly into the cavernous spaces without entering capillaries and then emptying into postcavernous venules (Figure 5.8). The helicine arteries appear tortuous and contracted when the penis is flaccid, becoming straight and larger in caliber during erection. The corkscrew-like shape ensures that flow is not compromised, allowing for elongation and dilatation. These arteries are surrounded by multiple layers of smooth muscle, which remains contracted during the non-erect state (allowing only small quantities of blood into the lacunar spaces).2,3,25
It is not uncommon for the erectile tissue to be primarily supplied by accessory arteries, such as the accessory pudendal artery. In fact, the dominant blood supply to the corpora may arise from the external iliac, obturator, vesical or femoral arteries, or even derive exclusively from a single (unilateral) cavernous or accessory pudendal artery. Careful preservation during radical prostatectomy is suggested for the accessory pudendal vessels, as this maneuver has been shown to protect, and hasten the recovery of, sexual function.

In addition to the cavernosal artery, the common penile branch of the internal pudendal artery branches in the anterior perineum into the dorsal artery of the penis and the bulbourethral artery. These vessels form a vascular ring near the glans; the paired dorsal arteries course within the neurovascular bundles at the eleven o’clock and one o’clock positions, lateral to the dorsal vein and medial to the dorsal nerves. The dorsal arteries supply the more superficial components of the penis; they supply the spongiosum distally via circumflex branches; they provide prenural branches; and they may contribute to the blood supply of the erectile bodies. They are also responsible for glans engorgement during erection. The bulbourethral artery continues as the urethral artery after its bulbar offshoot, coursing along the ventral surface of the corpus spongiosum beneath the tunica albuginea. Of note, given the blood supply to the glans, it can be completely separated from the corpora cavernosa during surgery without compromising vascularization.

Decreased perfusion pressure and arterial flow to sinusoidal spaces may occur, owing to atherosclerotic or traumatic arterial occlusive disease of the hypogastric–cavernous–helicine arterial tree; clinically, arterial disease may manifest itself as an increased time to maximal erection or as decreased rigidity. As the number of vascular risk factors increases (e.g. hypertension, hyperlipidemia, diabetes, and cigarette smoking), the occurrence of atherosclerotic lesions of the internal pudendal, common penile, and cavernous arteries increases significantly. On the other hand, a focal stenosis of the common penile or cavernous artery is most often seen in young patients who have sustained blunt perineal or pelvic trauma. Thus, both generalized and focal arterial disease may manifest itself as erectile dysfunction.

### Conclusion

The microanatomy of erectile function reflects the physiological changes necessary for the human penis to attain an erect state. Erection is dependent upon intact innervation and arterial supply, as well as on a normal cavernous smooth muscle response to stimuli and an efficient veno-occlusive trapping mechanism. During erection, the relaxation of smooth muscle in the cavernous trabeculae and arterial walls facilitates the complex cascade responsible for penile rigidity:

1. Increased penile blood flow caused by dilation of arterioles and arteries.
2. Expansion of sinusoids and resultant trapping of blood.
3. Compression of subtunical venous plexuses between the tunica albuginea and peripheral sinusoids, reducing venous outflow.
4. Tunica albuginea expansion, further decreasing venous outflow as emissary veins are occluded between inner circular and outer longitudinal layers.
5. Intracavernous pressure increase to approximately 100 mmHg (full erection phase).
6. Ischiocavernous muscle contraction, which further increases intracavernous pressures to several hundred mmHg (rigid erection phase).

Detumescence occurs as gradual smooth muscle contraction against a closed venous system causes a transient increase in
intracavernous pressure, followed by a slow pressure decrease as venous channels open with a resumption of basal arterial flow, and, finally, a rapid pressure decrease with fully restored capacity for venous outflow.

Whether isolated to a single element of penile microscopic anatomy or occurring on more than one tissue level, pathologic structural changes may compromise the physiologic processes that lead to penile erection, and so result in erectile dysfunction.

REFERENCES


Vascular physiology of erectile function

Noel N Kim

Introduction

The previous chapters on penile anatomy emphasize the importance of the vasculature in mediating erectile function. The penile corpora cavernosa are highly specialized vascular structures that are uniquely suited to their function of becoming engorged during sexual arousal. In addition, the network of resistance arterioles that carry blood to the corpora cavernosa plays an equally important role in determining the state of penile engorgement. In the non-aroused, flaccid state, the arterial and trabecular smooth muscle remain constricted, and the hemodynamic environment of the corpora cavernosa is similar to the venous circulation in terms of pressure, flow, and oxygen tension. There is low resistance to the drainage of blood from the cavernosal bodies, and this contributes to the maintenance of penile flaccidity.

The onset and maintenance of penile tumescence is initiated by central psychogenic or peripheral reflexogenic sensory stimuli (or both), as described in greater detail in the following chapters. Both central and peripheral pathways stimulate sacral parasympathetic efferent nerve fibers, which ultimately cause the relaxation of the vascular smooth muscle in the resistance arterial bed and the trabeculae of the corpora cavernosa. These events result in a higher rate of blood flow into the penis, and greatly increase the compliance of the cavernosal bodies, enabling expansion and accommodation of the increased blood volume within the cavernosal lacunae. The increased blood flow also potentiates local vasodilation through endothelial shear stress-induced responses. During this early filling phase, the hemodynamic environment within the erectile tissues transitions into an arterial system with respect to blood flow and oxygen tension. However, blood pressure remains low.

The rapid volume expansion of the erectile tissue leads to engagement of the veno-occlusive mechanism, reducing the outflow of blood. The restriction of blood drainage is accomplished by elongation and compression of the subtunical venules that are located between the corpora cavernosa and the tunica albuginea. Veno-occlusion enables the trapping of blood within the cavernosal sinusoids and causes the intracavernosal pressure to rise to systemic arterial levels. As the pressure gradient between the systemic arterial circulation and the intracavernosal vascular compartment is dissipated, blood flow decreases. Altogether, these events act in concert to achieve and maintain full tumescence and rigidity.

Thus, changes in smooth muscle tone are crucial for regulating erectile function. In that regard, continuing research to elucidate the myriad of mechanisms that regulates vascular smooth muscle cell (VSMC) contractility is essential to understanding erectile physiology. The basic paradigm of smooth muscle, endothelium, and nerve interactions to influence vascular reactivity is universally acknowledged, but warrants more detailed consideration within the context of genital tissues. This chapter describes the basic mechanisms that regulate VSMC contractility, including additional consideration of non-contractile responses in VSMCs. However, discussion of specific neurotransmitters, receptor pharmacology, and regulation of extracellular matrix by smooth muscle have been omitted, since these are addressed elsewhere in this book. While much of the information specific to genital tissue vascular physiology is derived from studies on penile corpus cavernosum, findings from cardiovascular research will also be presented to gain further insight into VSMC function.

Endothelium: an active regulator of vascular function

The endothelium consists of a monolayer of cells that forms a continuous surface, lining the vascular compartment throughout the body. The total mass of the endothelium has been estimated to be 500 g in the average adult human, the majority of which is contained in the pulmonary vasculature. Much like skin, the endothelium may be considered a single organ with multiple functions and differential responses that are dependent upon both the systemic and local environments. Among other functions, a healthy endothelium serves to provide an anti-thrombotic, anti-inflammatory, and anti-atherogenic surface while also regulating vascular tone and permeability. The importance of endothelial regulation can be better appreciated by considering pathological states that have in common dysfunctional endothelium. Endothelium-dependent relaxation of blood vessels has been shown to be compromised in animal models of atherosclerosis, hypertension, diabetes, aging, smoking, and renal failure. Thus, diseased or damaged endothelium has been proposed to be a major contributor to vascular insufficiency of genital tissues.

The endothelium produces many vasoactive compounds that can influence the contractile, trophic, or synthetic function
of vascular smooth muscle cells. Factors that cause relaxation include nitric oxide (NO), carbon monoxide, endothelium-derived hyperpolarizing factor, prostacyclin and endothelin (through ET<sub>α</sub> receptors). Factors that cause contraction include endoperoxides, thromboxane A<sub>2</sub>, superoxide anions, and endothelin (through ET<sub>α</sub> receptors). One of the more novel mechanisms of regulating endothelial signaling involves changes in the number of caveolae on the surface of endothelial cells. Caveolae are invaginated microdomains of plasma membrane that are rich in endothelial NO synthase and contain the family of transmembrane structural proteins known as caveolins, as well as cholesterol, sphingolipids, and glycosyl phosphatidylinositol-linked proteins. In addition, caveolae contain numerous other signaling proteins, such as receptors with seven-transmembrane domains, G proteins, adenyl cyclase, phospholipase C, protein kinase C, calcium pumps, and calcium channels. Thus, these specialized signaling regions have been termed transductosomes.<sup>5</sup>

### Multiple functions of vascular smooth muscle

As a major constituent and primary effector of the vascular structures in the genitals, the VSMC is highly adaptable and multi-functional. The two primary functions of VSMCs are contraction and synthesis or maintenance of extracellular matrix. In cell culture experiments, VSMCs have been characterized as having either ‘contractile’ or ‘synthetic’ functional phenotypes. However, these two categories are considered to be extremes that are manifested under in vitro conditions, and it is likely that a range of intermediary phenotypes exist in any given tissue in vivo. Increasingly, protein and gene expression studies are illustrating the ability of VSMCs to alter their cellular phenotypes in response to changes in their environment.<sup>6,7</sup> In addition, studies by developmental biologists indicate that VSMCs in different vascular beds may arise from varying cellular lineages (multiple sources of progenitor cells) and can be recruited from different locations in the developing embryo.<sup>8</sup> Furthermore, comparative studies have led investigators to speculate that lineage-specific differences in VSMC growth and transcriptional responses may persist beyond the early developmental period and into the adult organism.<sup>9</sup> It remains unclear as to what extent the observed heterogeneity of VSMCs is due to adaptation in altered cellular environments as opposed to differences in lineage. The apparent mosaic nature of smooth muscle throughout the body may account for some of the diversity in responses found in different vascular tissues in health and disease. Nevertheless, most VSMCs in peripheral blood vessels are derived from the mesoderm and exhibit a set of common characteristics.

### Co-ordinated regulation of vascular smooth muscle cells

Most VSMCs in blood vessels and in cavernosal tissues are not adjacent to, or in direct contact with, an endothelial cell or nerve terminus. However, the thickness of any arteriole or trabecular bundle is limited to several cell layers. Given this arrangement, intercellular communication, for the purpose of regulating smooth muscle tone in a co-ordinated fashion, can be accomplished by two general mechanisms:

- extracellular diffusion of vasoactive and trophic factors released by endothelium, nerves and smooth muscle (paracrine and autocrine regulation); and
- intracellular diffusion of second messengers from stimulated cells into adjacent cells by means of gap junctions.

These mechanisms are not mutually exclusive and it is likely that they act in complementary fashion to propagate regulatory signals.

Extracellular diffusion of regulatory substances requires sufficient concentrations to be secreted near a population of effector cells. The magnitude of the response is determined by the number of cells directly stimulated by the secreted substance. In contrast, intracellular propagation of signals across multiple cells through gap junctions does not require each responding cell to be activated by the initial stimulus. A single cell may be stimulated by a secreted substance and generate second messengers that can diffuse into neighboring cells. In this mechanism, the magnitude of response is directly proportional to the number of cells activated by the spread of intracellular messengers, rather than the number of cells directly stimulated by the secreted substance.

The structure and function of gap junctions in the vasculature have been studied for the past several decades. VSMCs and endothelial cells are known to form functional syncytia by virtue of junctional plaques in their plasma membranes.<sup>9,10</sup> These plaques contain hundreds to thousands of gap junction complexes. The diameters of plaques between VSMCs range from 0.2 µm to 0.5 µm, whereas those between endothelial cells have been observed to be up to twice as large.<sup>9</sup> The area of each junctional plaque may be important in determining the rate of signal propagation. Each gap junction channel is formed by the docking of two hemi-channels, each hemi-channel being contributed by an opposing cell. Hemi-channels are hexameric structures formed from connexins, a large family of proteins derived from multiple genes.<sup>11</sup> VSMCs have been shown to express connexin (Cx) 40 and Cx43, whereas endothelial cells express Cx37 in addition to Cx40 and Cx43.<sup>9</sup> Cx proteins apparently have relatively short half-lives with estimated cycling times of 1–5 hours.<sup>10</sup> This suggests that junctional plaques are highly dynamic structures that may have the ability to attenuate or potentiate smooth muscle responses.

While the role of most connexins has not been studied in genital tissues, the expression of Cx43 has been confirmed in smooth muscle and endothelial cells derived from human penile corpus cavernosum.<sup>9,10</sup> Furthermore, functional and pharmacological studies suggest that they play an important role in signal propagation.<sup>12</sup> In studies using non-genital tissues, junctional plaques between endothelial and smooth muscle cells have been observed.<sup>13,14</sup> However, the presence of these ‘myoendothelial’ gap junctions has not been studied in genital tissues and their significance remains unclear. Thus, gap junctions enable smooth muscle and endothelial cells to form a continuous network of functional units. These cellular networks can rapidly co-ordinate the response to various
stimuli that may not be homogeneously distributed throughout the tissue.

**Mechanism of smooth muscle contraction**

Generation of force by VSMCs is ultimately determined by the interaction between myosin cross-bridges and actin filaments.\(^{15-17}\) Numerous dense bodies consisting of alpha-actinin are distributed throughout the smooth muscle cell, either in the cytoplasm or associated with the plasma membrane. Analogous to the Z-disk structures in striated muscle, dense bodies provide points of anchorage for actin filaments and are themselves stabilized by a network of intermediate filaments that are composed of desmin and vimentin. Unlike striated muscle, the molecular contractile units of interdigitating actin (thin) filaments and myosin (thick) filaments are not regularly aligned with one another and can be oriented in multiple directions.

Smooth muscle myosin is a large hexameric protein, consisting of two heavy chains and four light chains. The heavy chains are identical and have both globular and linear domains. The linear domains contain the C-termini and form coiled-coil structures that result in the ‘tail’ of the myosin molecule, while the globular domains contain the N-termini and possess actin-binding sites and ATP catalytic activity (ATPase). These globular heads of the myosin molecule form the cross-bridges of the contractile apparatus. The four light chains in myosin consist of two essential light chains that have a molecular weight of 17 kDa each (ELC\(^{17}\)) and two regulatory light chains that have a molecular weight of 20 kDa each (MLC\(^{20}\)). One essential and one regulatory light chain is associated with each globular head in myosin. In smooth muscle, myosin molecules self-associate into a side-polar arrangement in which the globular heads protrude in a linear array on two opposing sides of the thick filament.\(^{18}\) On any given side, the globular heads are oriented in the same direction, but anti-parallel to those on the opposite side (Figure 6.1).

This is in contrast to skeletal muscle myosin, which has a bipolar helical arrangement, in which the globular heads protrude in a helical pattern around the thick filament and are oriented in opposite directions on either side of the M-line within the sarcomere. Actin filaments are composed of two long strands of globular actin that intertwine into a double helical arrangement. While troponins are absent in smooth muscle, other regulatory proteins such as caldesmon and calponin are known to be associated with actin. The potential roles of these proteins are discussed below, after a brief presentation of the cross-bridge cycle.

**The cross-bridge cycle and the central role of calcium**

The contractile response of the smooth muscle cell is tightly associated with the intracellular concentration of free calcium. However, intracellular calcium regulates the contractile apparatus in an indirect manner through the regulatory protein calmodulin, which has the capacity to bind four calcium ions. Calcium-bound calmodulin undergoes a conformational change and thereby increases its affinity for myosin light chain kinase (MLCK) and activates it. Calmodulin-activated MLCK then phosphorylates the serine-19 residue of MLC\(^{20}\). In the presence of ATP, this phosphorylation enables actin to activate the myosin ATPase and initiates cross-bridge cycling. Crystal structure studies of myosin complexed to analogs of ATP and the ATP–ADP transition state suggest that a single power stroke can achieve approximately 10 nm of linear displacement.\(^{19}\)

Beginning with a state in which myosin cross-bridges are bound to actin with high affinity in the absence of ATP, one complete cycle consists of the following events (Figure 6.2):

1. Phosphorylation of MLC\(^{20}\) by calcium–calmodulin–MLCK complex activates myosin ATPase
2. ATP binds the globular head of myosin and causes it to dissociate from the actin filament, changing the cross-bridge angle to prepare for the power stroke
3. In this dissociated state, myosin hydrolyzes ATP and rebinds with actin in a low affinity state
4. Release of the hydrolyzed inorganic phosphate increases the affinity of myosin for actin and generates the power stroke of the globular myosin head, shortening the contractile apparatus
5. Dissociation of ADP from myosin enables another molecule of ATP to bind the myosin cross-bridge and continue onto a second cycle.

This series of events continues until MLC\(^{20}\) is dephosphorylated by myosin light chain phosphatase (MLCP). Assuming that energy stores are not limiting, maintenance of high intracellular calcium concentrations ensures that MLCK remains active and perpetuates cross-bridge cycling.

**Molecules regulating the contractile apparatus**

Myosin light chain phosphatase and Rho-kinase

At any given level of intracellular calcium, the contractile apparatus may become further sensitized by the inhibition of MLCP, such that the rate of myosin dephosphorylation (inactivation) is reduced and the action of MLCK becomes more efficient. Thus, modulation of MLCP activity is thought to be important for regulating smooth muscle contraction. MLCP is a holoenzyme consisting of a type 1 phosphatase (PP1c-delta), a myosin-targeting subunit (MYPT-1 – also...

![Figure 6.1 Structure of myosin.](image-url)
called myosin binding subunit, MBS), and a 20 kD subunit of unknown function. The activity of MLCP can be modulated by a variety of factors. Two of the better-recognized mechanisms involve both direct and indirect effects of Rho–Rho-kinase pathway. Rho proteins are small GTPases classified as a subgroup of the Ras superfamily; they can be activated by the binding of agonists to G protein-coupled receptors. Activated Rho can in turn activate Rho-kinase, a serine–threonine kinase. Rho-kinase can then phosphorylate multiple substrates including MYPT1, the 17kD protein kinase C-potentiated inhibitor protein (CPI-17), and MLCP. Phosphorylation of MYPT-1 and CPI-17 results in the inhibition of PP1c-delta phosphatase activity, whereas phosphorylation of MLC would stimulate activation of myosin. The RhoA–Rho-kinase pathway and its effects on MLCP have been shown to play an important role in regulating smooth muscle contractility in both male and female genital smooth muscle. The presence of CPI-17 protein has been detected in human and rabbit penile corpus cavernosum, but its functional significance remains to be determined.

Actin-associated proteins
In as much as myosin may be considered the molecular motor that mediates contraction, experimental evidence suggests that cross-bridge cycling rates and tension development in smooth muscle are not necessarily proportional to MLC phosphorylation. These discrepancies are partially attributable to the presence of other proteins associated with actin that may regulate myosin–actin interactions. Included in this list of proteins are caldesmon, calponin, and tropomyosin. While much of the experimental evidence regarding these actin-associated molecules remains controversial, ignoring these potential regulatory mechanisms reduces our understanding of the contractile apparatus to an oversimplification.

Both caldesmon and calponin have the ability to bind actin and myosin and can inhibit myosin ATPase activity to suppress development of smooth muscle tone. Studies examining protein interactions also suggest that calponin may facilitate agonist-induced signal transduction by facilitating protein kinase C activation in the plasma membrane. Furthermore, calponin may mediate the targeting of extracellular regulated kinase and protein kinase C to the plasma membrane. Lastly, tropomyosin is intimately associated with actin filaments, forming a continuous strand made of coiled coil monomers. In the absence of troponins, smooth muscle tropomyosin appears to participate in co-operative interactions between actin and myosin, as well as with caldesmon. Thus, through changes in their associations between actin and myosin and other key signaling molecules, calponin, caldesmon, and tropomyosin may regulate cross-bridge cycling and VSMC tone in a manner that could not be accomplished by calcium alone.

**Latch: a unique characteristic of vascular smooth muscle cell contraction**
A hallmark of smooth muscle function is its ability to maintain tension for prolonged periods without a correspondingly high consumption of energy. Thus, the rate of ATP hydrolysis is not proportional to the number of myosin heads engaged in generating force. This efficiency in maintenance of tone has been termed the latch state, and is critical for sustaining the ‘basal’ non-aroused state in genital tissues, which requires the
smooth muscle to remain contracted for most of the time. The mechanism by which VSMCs can achieve latch remains unknown. However, decreased MLC$_{20}$ phosphorylation and low myosin ATPase activity have been associated with latch.\textsuperscript{15} In addition, after attaining the latch state, mammalian smooth muscle is not able to redevelop force when cross-bridges are subjected to a quick release by the addition of ATP in the absence of calcium. These data suggest that the latch state results from a decrease in the rate of cross-bridge detachment from the actin filament. Under normal physiological conditions, ATP availability is not restricted and any dephosphorylated myosin bound to actin in the high-affinity state would quickly bind ATP and dissociate from the actin filament. Thus, this mechanism could not account for a slow rate of cross-bridge detachment. For these reasons, it has been proposed that dephosphorylated myosin remains bound to actin in the high-affinity state while still binding ADP. This type of interaction could also facilitate cooperative attachment of non-phosphorylated myosin to actin to help to stabilize the latch state. Recently, it has been proposed that calponin participates in the latch state by simultaneously binding actin and myosin to stabilize cross-bridge interactions and slow the rate of detachment.\textsuperscript{28}

### Signal transduction pathways regulating vascular smooth muscle cell tone

Pathways that regulate smooth muscle contractility ultimately influence intracellular calcium levels or alter the calcium sensitivity of the contractile proteins (Figures 6.3 and 6.4). Thus, vasoactive substances, via pharmacomechanical coupling (contraction or relaxation in the absence of membrane potential changes), or changes in cell membrane potential, via electromechanical coupling, can change intracellular calcium concentrations, which regulate the contractile apparatus, as described previously. However, intracellular calcium concentrations need not change for contraction or relaxation to occur if the sensitivity of the contractile apparatus to calcium is changed. This additional mode of calcium-independent regulation can result in sensitization through inactivation of MLCP or desensitization through the inactivation of MLCK. Both phosphatase and kinase activity can be inhibited by phosphorylation events (e.g. phosphorylation of MLCP by Rho-kinase). In general, most vasoactive substances exert their effects...
through intracellular signaling mechanisms that involve at least some aspect of pharmacomechanical coupling. While an exhaustive review detailing the pharmacology of each vasoactive substance or class of receptors is beyond the scope of this chapter, key pathways that regulate smooth muscle tone are summarized in Figures 6.3 and 6.4.

Non-contractile responses in vascular smooth muscle cells

Changes in VSMC growth and extracellular matrix production can have a profound impact on the function of genital tissues. The extracellular matrix itself is a dynamic structure that plays an important role in modulating cell morphology, movement, growth, differentiation, and survival by regulating cell adhesion, cytoskeletal machinery, and intracellular signaling. It is possible that VSMCs may transform from primarily contractile cells into primarily synthetic cells (or vice versa) in response to changes in their environment (e.g., chronic disease states or acute injury). Alternatively, there may be an inherently heterogeneous population of VSMCs in a given vascular tissue.

In addition to growth factors and cytokines, vasoactive factors have also been shown to have trophic effects in the vasculature, suggesting that many of the same intracellular mediators that cause contraction or relaxation are also involved in trophic responses in VSMCs.

While the intracellular integration of various stimuli and co-ordination of responses is poorly understood, it is likely that the net response of any given VSMC is dependent upon the overall gene expression profile. Synthetic VSMCs are primarily characterized by a significantly decreased expression of contractile proteins. Thus, activation of pathways that may have mediated tonic responses in contractile VSMCs may modulate cell growth or matrix production in a synthetic VSMC.20

Many growth factors stimulate cell surface receptors with intrinsic tyrosine kinase activity in their cytoplasmic domains. This tyrosine kinase activity is considered essential for regulating cell growth. Several of these receptors have been linked with the activation of phospholipase C (PLC)-gamma. Also, phospholipase D may be more important for mediating trophic responses than contractile responses. Some variations in responses to growth factors and vasoactive substances may be due to the different mechanisms of activation for different

Figure 6.4 Signal transduction pathways regulating smooth muscle relaxation. Gray arrows indicate association, binding, or activation, whereas the clear arrow from “cAK” to “MLCK” indicates inhibitory regulation. Indirect or putative interactions are indicated by dashed arrows. Alpha, alpha subunit of G protein; AM, actin-myosin contractile apparatus; BK, calcium-activated maxi-potassium channel; cAK, cAMP-dependent protein kinase; cGK, CaMK, calmodulin-dependent kinase; cGKI, cGMP-dependent protein kinase type 1; cGKI-beta, beta isoform of cGKI; cGMP-dependent protein kinase; CO, carbon monoxide; HSP20, 20 kilodalton heat shock protein; IP, IP, receptor; IRAG, IP, R-associated cGK substrate; KATP, ATP-dependent potassium channel; MLCK, myosin light chain kinase; MLCP, phospholamban; SER, smooth endoplasmic reticulum; SERCA, SER calcium ATPase.
PLC isoforms. In addition to preferential activation of PLC-gamma by tyrosine kinases, the beta-1 and beta-3 isoforms of PLC are activated by the alpha-q subunit of G\textsubscript{s}, whereas the beta-2 and beta-3 isoforms can be activated by the beta-gamma subunits of G\textsubscript{s}. PLC activity gives rise to the formation of diacylglycerol and stimulation of protein kinase C. Protein kinase C activation has been shown to have both proliferative and anti-proliferative effects to platelet-derived growth factor, epidermal growth factor, and angiotensin II.\textsuperscript{56} While the reasons for these variable responses remain unclear, it must be stressed that multiple isoforms of protein kinase C exist and that each isoform has numerous substrates.

Aside from its effects on the contractile apparatus and ion channels, protein kinase C has also been shown to modulate DNA synthesis, potentially through the phosphorylation of transcription factors.\textsuperscript{50} Among the most intriguing of these is nucleolin, a multi-functional protein located primarily in the nucleolus. In addition to its activities as a regulator of ribosomal DNA transcription and ribosomal assembly, nucleolin has been shown to regulate DNA decondensation and act as a plasma membrane receptor and shuttling protein between the cell surface and the nucleus.\textsuperscript{51}

Summary and perspective

Although an impressive amount of knowledge has been accumulated regarding smooth muscle biology and vascular physiology, it is important to keep in mind that many questions still remain and are being actively investigated. While a central and enduring question has been how calcium can elicit different responses within a given cell, it is becoming more apparent that unique spatial and temporal differences in intracellular calcium flux play an important role in this regulation. Mechanistic questions still remain, even in the well-established field of contractile proteins. For example, the disassembly of the contractile apparatus within VSMCs transitioning from contractile to synthetic phenotypes is not clearly understood. Future studies in genital tissue physiology will benefit from the application of knowledge gained from the fields of smooth muscle and vascular biology.

REFERENCES

Central nervous system control of sexual function in males and females

Lesley Marson

Introduction

Several reviews that focus on the behavioral and neuroendocrine aspects of sexual function have been published. The emphasis of this chapter is on the brain and spinal control of erectile and ejaculatory reflexes in males, and it gives a brief overview of sexual function in females. For more information on female sexual function refer to selected reviews. The focus here is on neuroanatomical and neurophysiological studies, primarily performed in the rat. Much progress of the central nervous system (CNS) neurobiology and neuropharmacological control of erectile and ejaculatory function has been made over the past few decades primarily using rodent animal models in which many of the autonomic and somatic changes seen during sexual reflexes are similar to that reported in humans.

Initial studies attempting to understand the CNS organization of erectile and ejaculatory process were based on the results of fairly large lesions studies done in the 1960s, and the resultant effects of these lesions on sexual behavior. With the development of more sophisticated techniques an effort has been made to identify and characterize neurons and their pathways that are involved in various aspects of sexual behavior. Around 40 years ago, Frank Beach proposed a general framework for the central nervous organization of sexual function, which was based on his concepts and published research at that time (Figure 7.1). Beach proposed that hormonal and sensory inputs regulating sexual behavior were integrated in the forebrain. Forebrain nuclei relayed through the brainstem to the spinal cord and thus controlled the lower genital reflexes. The higher brain regions could initiate sexual behavior. Evidence for excitatory influences on sexual reflexes are evident from nocturnal erections and psychogenic erections. Beach also proposed that genital reflexes, such as erection and ejaculation, could be produced in response to genital stimulation even if the connections from the brain were severed from the spinal cord. Thus, peripheral genital stimulation enhances excitability within the spinal cord. The brain perceives and modulates sexual function but the spinal cord contains the neural circuits for erection, ejaculation, and climax. Evidence supporting this hypothesis came from spinal cord injured patients, in whom genital stimulation could still produce erections, and from spinalized experimental animals in which genital stimulation more easily produced sexual reflexes. These studies also implied that spinal sexual reflexes were primarily under inhibitory control from the brainstem (Figure 7.1). This framework still stands today and can also be applied to female sexual reflexes.

While some recent valuable insights using imaging techniques have been gained from studies in humans, much of what we know about the anatomy and physiology and the pharmacological control of the CNS pathways that regulate sexual function has relied on animal models. These findings indicate that multiple factors interact at supraspinal levels to influence the excitability of spinal reflexes. Sexual responses are under both voluntary and involuntary control, and significant changes occur during sexual activity, which depends on type and level of gonadal steroid hormones.

Models of erection and ejaculation

Study of sexual behavior and reflexes has necessitated the development of several models that exemplify various aspects of sexual reflexes. Undoubtedly the most complete way of examining sexual responses is to monitor sexual activity during sexual behavior or intercourse. Many laboratories use this approach to examine putative neurotransmitters and the role of selected brain regions in regulating sexual behavior. In addition to monitoring mounts, intromissions, ejaculations, and lordosis, aspects of motivational behavior, aggression, and reward systems can be assessed.

This chapter focuses on more reflex aspects of sexual function (i.e. the neurophysiology and neuroanatomy of genital reflexes) and in doing so outlines the CNS regions involved in the actual processing of these reflexes. Neurophysiological and neuroanatomical techniques often require surgical interventions or anesthetic to monitor the autonomic and somatic components of sexual reflexes. Thus complete parallelism with sexual behavior, especially in humans, cannot necessarily be confirmed. However, data gained from these types of studies have not only supported observations obtained from behavioral studies, but have also been paramount in discovering many of the neurobiological mechanisms that have aided understanding human sexual function and dysfunction.

Ex copula reflexes

Hart and Sachs described a preparation for eliciting penile reflexes in awake male rats. The rats are lightly restrained
in a supine position and the penile sheath retracted. This elicits, within a few minutes, clusters of penile reflexes, including erection of the penile body and glans. This response is greatly facilitated by spinal transection, indicative of a descending inhibition of sexual reflexes.

**Intracavernous pressure**

Intracavernous pressure recordings have been used as an index of penile erection, and valuable information on drug therapies to enhance erections has been gained using this model. When the intracavernous pressure (ICP) is increased, an erection occurs, because of increased blood flow within the penis. This model therefore measures erection but does not account for skeletal muscle contractions, which are required to provide a full rigid erection.

**The urethrogenital reflex**

Ejaculation is the expulsion of fluids from the urethra facilitated by rhythmic perineal muscle contractions. Closure of the bladder neck and urethral sphincter by sympathetic and somatic pathways prohibits retrograde ejaculation to the prostate and seminal vesicles, and prevents urine flow during ejaculation. The urerogenital (UG) reflex model was developed by McKenna and colleagues, in an attempt to develop a model of erection and ejaculation in which neurophysiological recordings could be made and examined in relationship to genital reflexes. The model comprises pudendal sensory nerve stimulation, which reliably evokes a co-ordinated response consisting of clonic contractions of the perineal muscles (the ischiocavernosus and bulbocavernous muscles), increases in ICP, rhythmic firing in the cavernous nerve, and expulsion of the urethral contents (ejaculation) (Figure 7.2).

Neurophysiological recordings in humans have shown concomitant rhythmic contractions of the perineal muscles with ejaculation, together with the sensation of orgasm/climax. Ischiocavernosus and bulbospongiosus muscle recordings have also been monitored during copulation in male rats, and these muscles fired in synchrony during mounting and intromission, and sometimes during ejaculation.

This model has also been used to examine the neurophysiological mechanisms involved in female sexual climax and represents changes in vaginal blood flow and pressure, and vasocongestion, as well as anal sphincter and pelvic floor contractions, many of which are associated with sexual arousal and climax in women.

The UG reflex is centrally generated and is triggered by a spinal pattern generator, which involves multiple spinal segments that co-ordinate somatic, sympathetic and parasympathetic activity of the sexual organs. There are many similarities between the UG reflex and sexual climax: they are relative insensitivity to gonadal hormones, both are the product of spinal generators, both require co-ordinated autonomic and somatic neural mechanisms, and the UG reflex and climax is similar in males and females.

**Forebrain regions involved in male sexual reflexes**

Early research studies confirmed that the forebrain was essential for male sexual behavior. In rodents, the olfactory
system is also important in sexual motivation. The olfactory-vomeronasal system sends direct inputs to the medial amygdala, which is important in sexual behavior in multiple species.43-45 The medial preoptic area (MPOA) receives inputs from the amygdala, and many studies have shown that the MPOA is necessary for the execution of male sexual behavior.46-48 Lesions of the MPOA and adjacent anterior hypothalamus caused copulation deficits in several species.34,49,50 Stimulation of the MPOA induced or facilitated sexual behavior and rhythmic firing of the pudendal motor nerve and penile erection (Figure 7.3).46,48,51-53 Electrical and chemical stimulation of the MPOA induced rhythmic firing of the pudendal motor nerve, indicative of the UG reflex (Figure 7.4).52

Since the MPOA does not project directly to the spinal cord regions that co-ordinate the sexual output, facilitation of sexual reflexes must relay through sites within the brain for the appropriate response to occur. Data from my laboratory and others suggest that the periaqueductal gray (PAG) is an important region containing the descending pathway from the MPOA to the spinal cord.53 Electrolytic lesions or lidocaine injections into the PAG blocked the MPOA-induced activation of the UG reflex, confirming that neurons in the MPOA project through the PAG to mediate the perineal muscle activity (Figure 7.5).53

In addition, a major neuroanatomical pathway from the MPOA through the PAG was mapped using neuroanatomical tracing techniques (Figure 7.6).41 The observation that activation of neurons in the MPOA initiates the UG reflex not only agrees with other published work, but also supports usefulness of the UG reflex model in elucidating some of the excitatory pathways involved in sexual function. The MPOA contains a high density of neurons that concentrate gonadal androgens, and it is extensively interconnected to many other brain regions, including the limbic system and lower autonomic brainstem nuclei.31,54-57 Therefore, the MPOA is capable of integrating sensory and hormonal signals that initiate sexual reflexes in males. Activation of the MPOA can also facilitate female sexual responses. However, MPOA lesions do not abolish erections evoked by masturbation and do not decrease sexual motivation, suggesting that other brain regions are important for other components of sexual behavior.58,59

Growing evidence suggests that the paraventricular nucleus of the hypothalamus (PVN) is important for penile erections. Stimulation of the PVN evokes erections in both awake and anesthetized rats, and lesions of the PVN decrease the proerectile effects of various compounds. One mechanism of PVN-mediated erections is activation of oxytocin neurons that project directly to the lumbarosacral spinal cord.60 Different brain pathways contribute to the regulation of the various components of sexual behavior; for example, PVN neurons

![Figure 7.3](image1)  
Figure 7.3 Photomicrograph illustrating the location of a DL-homocysteic acid injection (arrow) into the medial preoptic area that was successful in eliciting the urethrogenital (UG) reflex. The photomicrograph is superimposed onto a coronal section of the forebrain showing the adjacent brain structures. 3V, third ventricle; f, fornix; LPO, lateral preoptic area; MPA, medial preoptic area; MPO, medial preoptic nucleus; OX, optic chiasm; Sch, suprachiasmatic nucleus.

![Figure 7.4](image2)  
Figure 7.4 Polygraph tracing demonstrating the effect of bilateral electrical stimulation of the medial preoptic area (MPOA) on the urethrogenital (UG) reflex. The male rat was anesthetized and spinaly intact. Electrical stimulation of the MPOA (250 nA/0.2 msec pulses at 50 Hz, 1 sec on/off, indicated by the black bar in the timer trace). Note: blood pressure increase during the stimulation and the UG reflex (indicated by the coordinated rhythmic firing of the pudendal motor nerve branch) was present at the termination of the stimulus. From reference 53 with permission.
do not regulate mounting behavior, which may be primarily controlled by the MPOA.\textsuperscript{41}

Cortical activity was found following electrical stimulation of the dorsal nerve of the penis or clitoris.\textsuperscript{62,63} In humans, positron emission tomography and functional magnetic resonance imaging have been used to examine brain regions that show an increased cerebral blood flow during specific activities related to sexual function.\textsuperscript{64–66} These studies have primarily used visual sexual stimuli with arousal, but a few studies have examined areas specifically activated with vaginocervical stimulation and ejaculation/orgasm.\textsuperscript{65,66} Areas commonly activated with arousal include the anterior cingulate and insular cortex, striatum, amygdala, and hypothalamus. These sensory pathways may also be important in psychogenic sexual arousal and nocturnal erections. Additional areas activated with vaginocervical stimulation or ejaculation included the cerebellum, ventral tegmental area (VTA), and thalamus. Many of these brain regions are involved in sexual responses seen in animal models and are present and activated in transneuronal tracing and c-fos studies.

**C-fos studies**

Immunohistochemical staining for the transcription factor encoded by the immediate early gene, c-fos, have been used to identify brain neurons that are activated with visceral and sensory stimuli.\textsuperscript{67–71} However, these studies cannot distinguish between neurons that are activated in response to the initiation of sexual function and those that are involved in the execution of the response. Studies to date have identified neurons in the forebrain that are activated in response to mounts, intromissions, ejaculation, lordosis, and vaginocervical stimulation in rodents.\textsuperscript{70–74} These studies have confirmed the importance of the MPOA and PVN in sexual response, as well as the VTA and ventromedial nucleus of the hypothalamus (VMN), which is essential for lordosis. In addition, other areas within the forebrain have been identified that demonstrate increases in c-fos activity, which correlates to specific stages of sexual behavior. In summary, the bed nucleus of the stria terminalis (BNST) and the medial amygdala are thought to receive chemosensory signals that are processed through the accessory olfactory bulb, and the BNST is involved in sexual behavior related to previous sexual experiences. Consummatory sexual behavior increases neural activity in the MPOA and the subparafascicular thalamic nucleus (SPFp). The SPFp projects to the MPOA and posterior nucleus of the amygdala, where neural activity is abundant after copulation.\textsuperscript{70,71}

**Transneuronal tracing studies**

Pseudorabies virus (PRV) is an alpha-herpes virus that is transsynaptically transported within the CNS.\textsuperscript{75–77} The virus crosses synapses and is self-amplifying (as a result of nuclear replication) and is therefore extremely useful in mapping the CNS circuits that innervate a variety of peripheral organs.\textsuperscript{78} The virus is injected into a peripheral organ and is retrogradely transported through the ganglia and spinal cord to the brain. We have used this technique to map the CNS circuits that project to the penis, perineal muscles, vagina, and clitoris in rats (Figure 7.7)\textsuperscript{36,79–81}

Similar labeling patterns were seen in the brain after injections of the penis, perineal muscles, vagina and clitoris, suggesting a common hierarchical control over these pelvic organs. Neurons consistently labeled in the forebrain included the MPOA, the PVN (see Figure 7.7), the lateral hypothalamus, and the VTA.\textsuperscript{79,80} The VMN was labeled only in females. Increasing the survival time allows labeling of second- and third-order neurons, i.e. labeling of neurons that are in synaptic contact to the already retrogradely labeled neurons. Longer survival times labeled cells in the BNST and cortex, suggesting neurons in these forebrain areas project to hypothalamic neurons. In the brainstem, areas constantly labeled

![Figure 7.5](https://example.com/figure7.5.png)

**Figure 7.5** Photomicrograph and corresponding coronal diagram illustrating the regions of the periaqueductal gray (PAG) matter that, when damaged, blocked the medial preoptic area (MPOA)-initiated urethrogenital reflex. On the photograph, arrows show location of bilateral lidocaine injections that blocked the MPOA-initiated UG reflex; the diagram shows the lesion areas (black circles) that consistently blocked the output from the MPOA. 3, trigeminal nucleus; PAG, periaqueductal gray; ml, medial lemniscus; RN, red nucleus.
Forebrain regions, such as the amygdala, BNST, nucleus accumbens, and SPFp, appear to play a role in the execution and reward aspects of sexual function. Sexual function is probably initiated by separate excitatory pathways or via disinhibition of neurons that tonically inhibit sexual reflexes (e.g., via the nPGi).

**Summary**

The forebrain regions identified to date appear to regulate the initiation and execution of sexual function, and many brain regions contain neurons whose activity is modulated by pelvic sensory input. These areas in turn regulate autonomic and motor output that is characteristic of sexual behavior. The MPOA is important for the integration of sensory and hormonal signals related to sexual function; the PVN is important for penile erections; the VMN is essential for lordosis; other forebrain regions, such as the amygdala, BNST, nucleus accumbens, and SPFp, appear to play a role in the execution and reward aspects of sexual function. Sexual function is probably initiated by separate excitatory pathways or via disinhibition of neurons that tonically inhibit sexual reflexes (e.g., via the nPGi).

**Brainstem regions controlling sexual reflexes**

The UG reflex could not be elicited by genital stimulation in animals with intact spinal cords and, therefore, the UG reflex must be inhibited from a supraspinal site. This made this model ideal for isolating the inhibitory brain neurons. In a series of physiological, anatomical, and pharmacological...
The nPGi has long been thought to be involved in the regulation of cardiovascular systems and pain. However, this area has been shown to contain excitatory and inhibitory neurons that respond to genital stimulation and manipulations of the pelvic, pudendal, and dorsal nerve of the penis. Lesions of this area also facilitate ejaculatory sexual reflexes and improve ejaculatory performance. Excitatory and inhibitory neurons in the nPGi respond to genital stimulation in the female rat and to manipulations of the pelvic and pudendal nerves and the dorsal nerve of the penis in the male. These studies demonstrate that the nPGi tonically inhibits somatomotor output and receives sensory information related to sexual function. The nPGi receives inputs from the MPOA, the PVN, and the PAG. The PAG is important for sexual function, and is the major relay region for forebrain inputs as they descend to the spinal cord.

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Spinal and peripheral innervation

The internal reproductive organs and external genitalia are primarily regulated by three branches of the nervous system: parasympathetic (the pelvic nerve), sympathetic (the hypogastric nerve), and somatic (the pudendal nerve). In addition, the vagus nerve innervates the uterus and cervix and may relay viscerosensory inputs during sexual function, especially after spinal cord injury. Sexual reflexes include concomitant activation or inhibition of these nerves, and genital sensory input is received via these nerves. The autonomic and somatic innervation of the pelvic organs has been reviewed in detail by several authors\textsuperscript{3,4,50} and is thus only briefly summarized in this chapter.

Somatic control

The pudendal nerve provides efferent innervation of the striated perineal muscles: the ischiocavernosus, the bulbospongiosus (also known as the bulbocavernosus), the ischiourethralis, and the external anal and urethral sphincters. Pudendal motor neurons – the dorsolateral (DL) nucleus and dorsomedial (DM) nucleus, also called the spinal nucleus of the bulbocavernosus – in the rat are located in the L5 and L6 segments of the spinal cord. The pudendal motor neurons in non-rodent species examined to date, are located in Onuf’s nucleus. The afferent spinal innervation of the pudendal sensory branch arises from the dorsal root ganglion (DRG) in L6 and S1 segments. These primary afferents terminate in the medial edge of the dorsal horn, on both sides of the spinal cord, and the midline dorsal gray commissure (DGC).

Autonomic control

The preganglionic neurons (PGNs) of the pelvic nerve are located in the intermediolateral column (IML, also called the sacral parasympathetic nucleus) in the L6–S1 segments of the spinal cord. Dendrites of the PGNs extend medially, into the lateral funiculus, and dorsally, along the lateral edge of the dorsal horn. The afferent (sensory) fibers of the pelvic nerve are found in Lissauer’s tract and along the medial and the lateral edge of the dorsal horn. The sympathetic PGNs of the hypogastric nerve are located bilaterally in the IML and DGC, in spinal segments T13–L2. Only a few hypogastric afferent fibers have been found in the superficial lateral and medial margins of the dorsal horn. The cavernous nerve is important in the mediation of the vasodilatory component of penile erection and vasocongestion of the clitoris.

Sensory mechanisms

The pelvic and hypogastric nerves convey sensory information primarily from the internal pelvic organs, while the somatic innervation from the genitals and skeletal muscles is provided by the pudendal nerve. The hypogastric, pelvic, and pudendal nerve afferents are sensitive to circulating gonadal steroid hormones. The autonomic afferents relay sensory and nocuous information from the internal genital organs, vagina, and skin.\textsuperscript{106,107} The pudendal inputs regulate the level of sexual receptivity received from peripheral stimulation and can...
Involved in genital function, and these studies have shown that afferents synapse on multiple interneurons in the spinal cord, which then relay through a spinal pattern generator, PGNs, and motor neurons to mediate the appropriate output. Stimulation of genital afferents results in labeled neurons in the medial dorsal horn, the DGC, the intermediate gray matter, and the lateral gray matter (Figure 7.9), and the putative neurotransmitters involved in relaying this activity have been mapped. The distribution of interneurons is consistent with the distribution of pelvic sensory terminals and is similar in males and females.\textsuperscript{40,42,111} Transneuronal tracing studies found the majority of labeled spinal neurons in the DGC and in the vicinity of the IML of the thoracic–lumbar sacral cord, similar to that seen in the c-fos studies.\textsuperscript{40,41,90} This complex system allows co-ordination of sexual reflexes and inhibition of bladder function.

One group of neurons in the lumbar medial gray matter has been shown to be critical for ejaculation in rats.\textsuperscript{112,113} These neurons (termed LSt cells) project to the thalamus and contain galanin and are activated specifically with ejaculatory behavior and with the UG reflex in males but not in females.\textsuperscript{40,42,112}

Neurotransmitters

Pharmacological studies have shown that many neurotransmitters act in the brain and spinal cord to modulate male and female sexual behavior. For further information on specific neurotransmitters, the reader should examine reviews on the specific compound of interest.

Briefly, serotonin has both a facilitatory and inhibitory effect on sexual function, and different receptor subtypes regulate various components of sexual behavior. Increased levels of serotonin in the CNS resulting from serotonin uptake inhibitors mediate the high incidence of orgasmic dysfunction seen with antidepressant therapy in humans and delay ejaculation in rats.\textsuperscript{86,114–117}

Dopamine has a facilitatory effect on sexual behavior and sexual motivation associated with reward in both males and females via its action on brain reward pathways (e.g. the amygdala, the nucleus accumbens, the hypothalamus, the VTA).\textsuperscript{119} Multiple neurotransmitters (e.g. glutamate, serotonin, nitric oxide, and oxytocin) interact with the dopamine pathways that are involved in sexual function.\textsuperscript{118} Noradrenergic fibers are abundant in spinal regions that regulate pelvic function, and electrophysiological studies have shown that adrenergic drugs alter the activity of the hypogastric, pelvic, and pudendal nerves.\textsuperscript{119,120} Administration of clonidine inhibits erections, penile reflexes, and vaginal blood flow; and intrathecal infusion of norepinephrine accelerates pelvic thrusting, suggesting a facilitatory effect of the exogenous drug on the activity of lumbosacral motoneurons.

Oxytocin is released during sexual behavior, and administration of oxytocin (into the MPOA or VMN) facilities female sexual behavior and elicits penile erections.\textsuperscript{50,121} Melanocortin acts via the CNS to stimulate arousal behaviors and penile erections\textsuperscript{122–124} via melanocortin 3 and melanocortin 4 receptors in the VMN, PVN, and spinal cord.

Spinal pathways

Intrinsic spinal pathways are vital for relaying and translating the peripheral sensory inputs to the appropriate efferent output (e.g. genital stimulation leads to genital arousal and the cognitive associated mood changes). In addition, psychogenic erections are initiated in sensory brain systems, which then relay to the arousal and erectile centers in the spinal cord. Sexual responses comprise a co-ordinated activation of sympathetic, parasympathetic, and somatic output, and the spinal cord circuits and pathways function as the spinal pattern generator for these responses.

A number of neuroanatomical and electrophysiological studies have examined the location of spinal interneurons
Summary

This chapter has attempted to summarize what is presently known about the CNS regions that regulate sexual responses. Over the past 50 years there has been an increasing volume of research on the neural control of sexual function, using a variety of approaches, which has resulted in the identification of several specific brain nuclei and pathways that regulate sexual responses in males and females. Neuroanatomical techniques (c-fos, transneuronal tracing) have allowed visualization of the neurons that are activated with specific components of sexual function. Brain imaging techniques have also provided important information, allowing correlation with animal studies.

Sexual reflexes are regulated by highly integrated spinal and brain autonomic and somatic pathways (Figure 7.10). The MPOA is important for the integration of sensory and hormonal signals related to sexual function; the cortex, amygdala, BNST, and thalamus play a role in the execution and reward aspects of sexual function. The PVN and VMN play an important role in penile erection and lordosis, respectively. Many of these brain nuclei project to and relay through the PAG and medullary reticular formation, although there is a direct innervation to the lumbosacral cord from the PVN. The spinal cord pathways, especially those mediating the physiological changes associated with the UG reflex, are tonically inhibited by neurons in the nPGi. Many of these brain regions also receive ascending sensory inputs from the pelvic, pudendal, and hypogastric nerves.

Acknowledgments

I would like to thank Dr Kevin McKenna, Marsha List, Jennifer Bradley, Karla Gravitt, Jessica Weidey, and Dr Rong Cai for their contributions to the research.

REFERENCES

118. Dominguez JM, Hull EM. Dopamine, the medial preoptic area, and male sexual behavior. Physiol Behav 2005; 86: 356–68.
Introduction

Over 200 years ago, the renowned English surgeon John Hunter provided the first insights into the physiology of ejaculation and, in particular, the role of the seminal vesicles during this phenomenon. He sought to explain why the consistency of the ejaculate differed depending on the timing of discharge from the penis, noting that initially semen was like ‘cream’ but then turned ‘less viscid’ as the discharge continued. He even went to the extremes of scientific endeavor by dissecting a man immediately after he was killed by a cannon ball, in order to identify further the precise anatomy of the ejaculatory mechanism and prove that the consistency of semen found in post mortem examinations was not due to autolysis.¹

Since the days of John Hunter, ejaculatory dysfunction is recognized as the most prevalent male sexual disorder.² This fact, along with major advancements in technology, have led us to a greater understanding of the physiology of ejaculation and have consequently provided new insights into potential treatments for ejaculatory dysfunction.

The process of ejaculation consists of two major phases: emission and expulsion. Emission refers to the deposition of sperm into the posterior urethra, where it forms ejaculate upon mixing with secretions from the prostate gland and seminal vesicles. Next, expulsion consists of the rhythmic antegrade advancement of the semen through the urethra and out the penile meatus. These two elements are mediated by a complex interplay between various somatic, sympathetic, and parasympathetic elements of the nervous system.³ This chapter discusses the basic components of the ejaculatory reflex, beginning with the initial sensory stimuli and ending with ejaculation proper. A brief review of the putative neurotransmitters affecting ejaculation is included at the end of the chapter.

Stimulation and receptors

The exact nature of the afferent stimuli that are necessary to trigger ejaculation are not well documented but most likely involve some combination of somatosensory, visceral sensory, and proprioceptive inputs.⁴ Direct sensory input is accomplished through stimulation of various receptors located mostly in the glans penis, but also in surrounding structures such as the penile shaft, perineum, testes, scrotum, and anal sphincter, among others. There are several types of receptors present in the glans penis, but most numerous are the free nerve endings that can sense deep pressure and pain. In a study conducted by Halata and Munger, it was observed that free nerve endings are present in almost every dermal papilla as well as scattered throughout the deeper dermis of the human glans penis.⁵ In addition, Pacinian and Ruffini corpuscles have also been identified to a lesser extent (with a 10:1 ratio of free nerve endings to corpuscles), though their significance is not well documented.⁶

Although the penis contains a high density of sensory fibers, tactile sensitivity is relatively low compared with other parts of the body.⁷,⁸ For example, typical cutaneous mechanoreceptors such as Meissner’s and Merkel cell corpuscles, which are well represented in the glabrous skin of the digits, are rare, if not completely absent, in the glans. An exception to this rule is the transitional region located between the external and internal surface of the prepuce that is continuous with the frenulum and removed with circumcision. This area has a high density of fine-touch neuroreceptors, including Meissner’s corpuscles.⁹

Early research based on histological studies hypothesized that patients with premature ejaculation had higher penile sensitivities. However, this postulate has recently been contradicted by a human study, which revealed no correlation between ejaculatory latency time and penile sensitivity measured with a vibrometer.⁶

Afferent pathway

The majority of free nerve endings identified in the penis are projections from small myelinated and unmyelinated A-δ or C nerve fibers.¹⁰ Sensory stimuli from these nerves travel along the dorsal nerve of the penis, a sensory branch of the pudendal nerve. After joining the pudendal nerve, signals travel to the lower lumbar and upper sacral segments (L6–S1) of the spinal cord.¹¹ From here, sensory stimuli are conducted through the lumbar spinothalamic cells (a population of specialized interneurons in the spinal cord, collectively referred to as the ejaculatory generator) and projected on the thalamus via the spinothalamic tract. Preliminary studies suggest that the lumbar spinothalamic cells are only activated at the onset of ejaculation. In addition to this major pudendal nerve input, there are a number of animal studies that implicate the pelvic and hypogastric nerves in relaying pre-ejaculatory sensory
signals, though they appear to be more involved in the sympathetic control of ejaculation.\(^4\)

### Central control of ejaculation

It is well appreciated that higher centers of the brain receive sensory information related to ejaculation, but the precise neuronal pathways for processing and relaying ejaculatory sensory information after it reaches the thalamus have yet to be identified.\(^4\) Several animal studies employing Fos expression as a signal marker for areas of the brain that are active during ejaculation have revealed a sub-circuit during male sexual activity that corresponds to ejaculation alone.\(^4\) Specifically, the posterior dorsal preoptic nucleus, the bed nucleus of the stria terminalis, the medial amygdala, and the posterior thalamus are the regions that show substantial neural activation with ejaculation (see Figure 8.1).\(^9\)

After the processing of ejaculatory sensory stimuli in the supraspinal sub-circuit, additional regions of the brain exert descending inhibitory or excitatory control on the spinal ejaculatory generator. These sites, identified as the medial preoptic area (MPOA), the paraventricular nucleus of the hypothalamus (PVN), and the nucleus paragigantocellularis (nPGi), act in concert with each other to modulate the ejaculatory phenomenon.

The nPGi projects to the pelvic efferents and interneurons in the lumbosacral spinal cord and exerts powerful inhibitory effects on the spinal ejaculatory generator, employing serotonin (5-hydroxytryptamine or 5-HT) as its neurotransmitter.\(^4\) The urethrogenital reflex cannot be elicited in intact rats without first performing thoracic spinal transection or producing a lesion in the nPGi. Furthermore, numerous studies have confirmed that lesions of the nPGi facilitated ejaculation in copulating rats.\(^10\)

On the other hand, the MPOA has well-documented excitatory effects on ejaculation. In several studies, both phases of ejaculation were abolished with lesions inflicted upon the MPOA.\(^11\) Moreover, electrical stimulation of the MPOA elicits ejaculation. This region of the hypothalamus has not been shown to have direct connections with the lumbosacral spinal cord area, but rather projects heavily on the nPGi via the periaqueductal gray matter. The MPOA is hypothesized to lower the ejaculatory threshold by removing tonic inhibition on the spinal ejaculatory generator by the nPGi.\(^12\)

The full significance of the PVN is still being investigated, but this pathway contains oxytocin as its neurotransmitter and is considered to have an overall excitatory effect on ejaculation. Fibers from the PVN project directly to autonomic preganglionic neurons in the lumbosacral spinal cord and pudendal motor neurons located in the L5–L6 spinal segment of the rat.\(^13\) Stimulating the PVN elicits both erection and ejaculation; however, a lesion of this nucleus does not preclude erection or ejaculation.\(^4\)

### The spinal ejaculatory generator

Despite supraspinal influence, the ejaculatory phenomenon is largely a spinal reflex. Perhaps the best evidence to support this precept is the ability to induce ejaculation spontaneously in patients that have had a complete spinal transection at T10 or above.\(^14\) In these spinal cord injury (SCI) patients, activation of this reflex arc depends largely on the intensity of the afferent input. It has been shown that SCI patients who fail to respond to vibratory stimulation for ejaculation using a single vibrostimulator may indeed successfully ejaculate with the use of additional vibrostimulators (see Figure 8.2).\(^15\)

The spinal ejaculatory generator is the synchronization center for ejaculation. Its fundamental role lies in the integration of both central and peripheral inputs to construct a well-co-ordinated output to the genitilia and surrounding structures, to allow for normal ejaculation.\(^16\) Given that ejaculation can occur in the absence of supraspinal input, this discussion of the reflex arc will begin where we left off, with the arrival of the sensory stimuli at the spinal ejaculatory generator.

As previously discussed, the spinal ejaculatory generator is made up of highly specialized interneurons called lumbar spinothalamic cells. A selective lesion to these cells will eliminate ejaculation without affecting other aspects of sexual behavior.\(^4\) Lumbar spinothalamic cells were previously noted to have afferent projections to the thalamus. In addition, these cells also have efferent projections to:

- the sacral parasympathetic nucleus, which contains viscera motor neurons that travel mainly in the pelvic nerves and control a variety of visceral pelvic organ functions\(^4\)
- the sympathetic preganglionic neurons (the dorsal central nucleus and the intermediolateral cell column), located at
spinal levels T12–L2, where they send postganglionic fibers to the pelvis via the hypogastric and to a lesser extent the pelvic nerve.\(^7\)

- the bulbospongiosus motor neurons (Onuf’s nucleus), located in the anterior horn of spinal segments S2–S4. This nucleus harbors the pudendal motor neurons that innervate the striated muscles involved in ejaculation – specifically, the bulbospongiosus, ishiocavernosus, and transverse perineal muscles.\(^4,17\)

**Efferent pathway and end-organs**

The emission pattern of ejaculation in humans consists of an interplay between parasympathetic and sympathetic outputs that involve a co-ordinated closure of the bladder neck and contraction of the seminal vesicles, vas deferens, and prostate. In animal models, bladder neck closure is solely under sympathetic control.\(^5,18\) However, the seminal tract is under dual innervation, with the parasympathetic nerves stimulating glandular secretion and the sympathetic nerves inducing smooth muscle contraction.\(^16\)

The sympathetic projections that control emission originate in cell bodies located in the lateral column of the thoracolumbar spinal cord and project to the sympathetic chains bilaterally at the level of T12–L2. From the sympathetic chain, the nerves then travel through several plexuses or the splanchic nerves (or both) to reach the superior hypogastric plexus, below the bifurcation of the aorta. From the superior hypogastric plexus, paired hypogastric nerves proceed to join the pelvic nerve and form the pelvic plexus.

The pelvic plexus represents the integration center for sympathetic and parasympathetic fibers. The parasympathetic fibers arise from the sacral plexus at levels S2–S4. From here, they travel via the pelvic nerve to the pelvic plexus to be integrated with sympathetic impulses. Branches from the pelvic plexus innervate the bladder neck, seminal vesicles, prostate, vas deferens, epididymis, and urethra.\(^19\)

Alpha-adrenergic receptors are involved in both central nervous system-controlled bulbospongious muscle contractions and peripherally induced seminal vesicle contractions. Support for the first statement derives from a study that demonstrated that intraventricular injection of 8-hydroxy-2-(di-n-propylamino)tetralin induced bulbospongious muscle contractions that were partially inhibited by intravenous administration of tamsulosin, an alpha-blocker.\(^20\) Support for the second statement comes from findings that abnormal ejaculation associated with alpha-blockers is also observed in SCI patients.\(^21\) Additionally, seminal vesicles express alpha-1 adrenoreceptors at the mRNA level, with alpha-1A, alpha-1B and alpha-1D subtypes being present in a 75:11:7:13.3 ratio; this distribution explains in part the ejaculatory disturbances clinically observed, with various alpha-blockers having different affinities for each of the alpha-adrenergic receptor subtypes.\(^22,23\)

In response to sympathetic stimuli arriving via the hypogastric nerves, postganglionic neurons that project onto the seminal tract release norepinephrine. Norepinephrine activates alpha-1-adrenergic receptors, increasing levels of calcium and actin–myosin interaction. This causes smooth muscle contractions of the vas deferens, an increase in luminal pressure in the cauda epididymis and proximal vas, and antegrade propulsion of spermatozoa into the ampulla of the vas. The distention of the ampullary wall of the vas deferens causes a nerve impulse that elicits contraction and thus movement of the seminal contents into the posterior urethra.\(^19\) Simultaneously, the sympathetic impulses elicit ejection of prostatic and seminal vesicle fluid into the posterior urethra, thereby completing the emission phase of ejaculation.\(^4\)

The expulsion phase of ejaculation involves somatic motor neurons whose major role is to facilitate the antegrade propulsion of semen out of the urethra. Although the efferent nerves in this reflex are somatic and thus innervate striated muscle, expulsion is largely under the influence of the autonomic nervous system which acts through the spinal ejaculatory generator’s projections upon Onuf’s nucleus.\(^24\)

By careful measurements of perineal muscle activity in human subjects, it has been revealed that during the expulsion phase there is synchronous activation of the ischiocavernosus, bulbospongious, and levator ani muscles, with contraction of the external anal and urethral sphincters.\(^16,25,26\) Typically, an ejaculatory response will provoke between 10 and 15 contractions. These contractions are regular and are initially spaced 0.6 seconds apart with subsequent intervals increasing by 0.1 seconds.\(^25\) It is of interest to note that contractions of the striated muscles occur concurrently with the pleasurable sensation referred to as orgasm.\(^26\) Similarly, increased contractions of the anterior abdominal wall musculature have been electromyographically recorded during ejaculation.\(^27\)
The concept that a high-pressure chamber develops in the prostatic urethra during the emission phase before the forward propulsion of the ejaculate has only been recently documented. In 2000, the pressure profiles throughout the different urethral segments were registered in five healthy male volunteers undergoing ejaculation. These sophisticated measurements were performed using a 10F balloon catheter with pressure transducers along the catheter from the bladder neck to the external sphincter. Pressure readings over 500 cmH₂O have been measured in the proximal urethra while the pressure distal to verumontanum never exceeded 400 cmH₂O. These findings support the concept that the ejaculate propelled through the urethra follows a pressure gradient, which prevents retrograde ejaculation.²⁸ It has also been documented that prostatic vascular flow in men dramatically increases after ejaculation and continues for at least 24 hours after each ejaculation.²⁹ Hence, frequent ejaculation may indeed be related to overall prostatic health. Another complementary urethral pressure study conducted in mongrel dogs collected simultaneous recordings of prostatic tissue electrical activity. Simultaneous increases in prostatic electromyographic activity and pressure were recorded with each ejaculatory spurt. This study elegantly proves that the prostate contracts during each ejaculation pushing out retained prostatic secretions.²⁸

To hark back to the days of John Hunter, further research has uncovered much information about ejaculation and, consequently, the reason why ejaculation becomes less viscous further along in expulsion.¹¹ The sequential release of accessory gland secretions (seminal plasma) gives rise to the majority of the content of semen, while spermatozoa provides less than 5% of total ejaculate volume. The purpose of the seminal plasma is to provide a protective and nutritious medium for the sperms' travel through the hostile acidic environment of the female reproductive tract. The average volume of male human ejaculate is 2–5 ml, the volume coming primarily from the contributions of the seminal vesicles, prostate gland, and bulbourethral glands. The first fractions of the ejaculate are rich in sperm and in prostatic secretions. Major portions of the later fractions of ejaculate come from the seminal vesicles, which provides the main energy source for the sperm in the form of fructose.

**Neurotransmitters and ejaculation**

There are numerous neurotransmitter systems involved in the ejaculatory phenomenon at both the spinal and supraspinal levels. The central serotonergic and dopaminergic neurons are considered by most authorities to have the most significant role,²⁶ whereas acetylcholine, epinephrine, neuropeptides, oxytocin, gamma-aminobutyric acid, and nitric oxide (NO) have all been shown to play a secondary role. As with most aspects of ejaculation, the neurochemical pathways are extremely complex and difficult to study, making it challenging to identify the precise role of each neurotransmitter in the ejaculatory process. Discussion of each neurotransmitter involved in the ejaculatory mechanism is beyond the scope of this chapter. Therefore, focus is directed toward three recognized, clinically important neurotransmitters: dopamine, serotonin, and NO.

**Dopamine**

Dopamine is generally considered to have a primary and facilitative role in ejaculation. In rat studies, dopamine levels originating from the MPOA progressively increase during copulation, culminating in ejaculation.²⁸ It is important to note, however, that five subtypes of dopamine receptors exist, making it difficult to identify the precise dopamine subtype involved in ejaculation. The dopamine receptors are generally classified into two major groups: D1-like receptors (D1 and D5) and D2-like receptors (D2, D3, and D4). To exemplify this point, it has been shown that stimulation of MPOA D2–D3 receptors by the D2–D3 agonist quinolone promotes seminal emission and ejaculation in rats.³⁷ In another investigation, a microinjection of a non-selective dopamine antagonist into the MPOA reduced the ejaculatory response.³⁸ In another study, intracerebroventricularly delivered 7-hydroxy-2-((di-n-propylamino) tetralin induced rhythmic bulbospongious muscle contractions and ejaculation. In this study the effect of 7-hydroxy-2-((di-n-propylamino) tetralin was inhibited by co-injection of a non-selective D2–D3 antagonist and a D3
antagonist, but not by injection of a preferential D2 antagonist. The authors suggest that targeting D3 receptors alone may provide a therapeutic approach for treating many ejaculatory disorders in humans.39 This study had an ancillary observation regarding bulbospongious muscle contractions, which have the same organized pattern of contractions for different doses of 7-hydroxy-2-(di-n-propylamino) tetralin. These results suggest that once the threshold for brain D3 receptor stimulation is reached, there is a programmed response, probably handled at the spinal level.39 This finding may have profound implications regarding the neurobiological basis for studying and treating premature ejaculation.

Serotonin

Perhaps the most studied neurotransmitter with regard to ejaculation is 5-hydroxytryptamine (5-HT), also known as serotonin. There are 15 different known 5-HT receptor subtypes, which are grouped into seven major classes (5HT1-7), with each one having a different location and function. With the exception of the 5-HT1A receptor, all receptors are coupled to secondary messengers by G proteins. Recognized 5-HT receptors that are important for ejaculation include the somatodendritic autoreceptors (5-HT1A), the presynaptic autoreceptors (5-HT1B, 5-HT1C), the signaling receptors (5-HT2A), and the reuptake transporters. Each one of these receptors plays a specific role in the activation and cell signaling of the serotonin system with regard to ejaculation.40 Many of these 5-HT receptor subtypes are localized in the thoracolumbosacral cord, in addition to higher centers, the vas deferens, and the seminal vesicles.41

The 5-HT1A somatodendritic autoreceptors in the mesencephalic and medullary raphe, when stimulated, are responsible for decreasing 5-HT release into the synapse and thereby reducing ejaculatory latency through a negative feedback mechanism.41 In contrast to the somatodendritic 5-HT1A receptors, presynaptic and postsynaptic 5-HT1B and postsynaptic 5-HT2 receptors are responsible for decreasing ejaculatory behavior in rats.16 Since the early 1980s, it has been well known that increasing 5-HT levels inhibits the ejaculatory reflex in laboratory animals. Central injection of 5-HT and systemic injection of the 5-HT precursor 5-hydroxytryptophan causes delayed ejaculation in rats, and the increased activation of postsynaptic 5-HT1B or 5-HT2 receptors (or both) most probably mediate this effect.41

Under normal circumstances, 5-HT is released from axon terminals; it binds to nearby serotonin receptors, induces a variety of effects, and is then quickly removed from the extracellular space by 5-HT transporters. The concept that people with premature ejaculation might benefit from increased extracellular 5-HT levels emerged from the clinical observations of depressed patients on selective serotonin reuptake inhibitors (SSRIs). SSRIs act by blocking 5-HT transporters, thus increasing the concentration of 5-HT by between two- and four-fold in the synapse, as measured by microdialysis experiments in rats.42 Indeed, some studies reported complete abolition of ejaculation with acute administration of SSRIs; however, many other studies failed to replicate these results with acute administration of SSRIs.43 With chronic use (2-6 weeks), the 5-HT1A receptor becomes desensitized, thereby allowing SSRIs to have their effect of delaying ejaculation. Although these findings give us an explanation as to why SSRIs are effective with chronic treatment, it does not clarify the reason why they are not effective in the acute phase, as high extracellular 5-HT concentrations are achieved with acute administration of SSRIs.

One hypothesis implicated the involvement of oxytocin in SSRI-induced delayed ejaculation.44 Two oxytocinergic neuronal systems in the central nervous system can be distinguished: the magnocellular and the parvocellular. Magnocellular systems are located in the hypothalamic supraoptic nucleus and in the anterior and posterior paraventricular hypothalamic nucleus. 5-HT is one of a range of neurotransmitters that modulate oxytocin release, and all oxytocinergic cell groups receive some serotonergic activation, mainly originating from the dorsal and median raphe nuclei in the brainstem. It has been documented that intracerebroventricular injection of 5-HT, systemic injection of the 5-HT releaser (fenfluramine or p-chloroamphetamine), and systemic injection of 8-OH-DPAT (8-hydroxy-2-(di-n-propylamino)tetraline), a selective 5-HT1A receptor agonist, causes significant increase in oxytocin release through activation of several subtypes of 5-HT receptors, among which 5-HT1A receptors located on the cell body of oxytocinergic neurons are the most extensively studied. Although the exact mechanism is unknown, it has been documented that oxytocin levels are elevated with sexual arousal and ejaculation. High oxytocin levels reduce the number of intromissions required for ejaculation, shorten the ejaculatory latency time, and decrease the time to semen emission in different species. Hence, it is hypothesized that high 5-HT levels, caused by SSRIs, also stimulate the 5-HT1A receptors located on the oxytocinergic neurons, which cause oxytocin release and has a proejaculatory effect. This phenomenon counteracts the delaying effect of 5-HT on ejaculation, through 5-HT1B and 5-HT2 receptors activation. As the 5-HT1A receptors become desensitized from the consistently high 5-HT levels, oxytocin secretion diminishes and the delaying effect on ejaculation by SSRIs ensues.44

Furthermore, 5-HT1A receptors located in different locations, such as the brain, raphe nuclei, spinal cord, and autonomic ganglia, may have different effects on the ejaculatory process.45 In summary, given the relationship between the serotonergic system and the excitatory or inhibitory effect on ejaculation, it is likely that ejaculatory disorders are caused by altered levels of 5-HT or altered sensitivity of the ejaculatory modulating centers in the central nervous system.44 This hypothesis provides the pathophysical basis for many of the ejaculatory disorders, though further investigation is indisputably required.

Nitric oxide

Recently, PDE-5 inhibitors have gained attention in the treatment of premature ejaculation, drawing attention to the role of NO in the ejaculatory mechanism. In the late 1990s, it was postulated that elevated levels of NO in the MPOA accelerated dopamine release and facilitated the male copulatory behavior of rats. It has been documented that microinjections...
with a NO synthase inhibitor, N-nitro-L-arginine methyl ester, decreased the number of erections, but also increased the number of seminal emissions in male rats.\textsuperscript{36,47} Further support comes from studies involving mice lacking endothelial nitric oxide synthase (eNOS/\textsuperscript{-/-} mice). It has been shown that these mice ejaculate with a shorter latency period and require less stimulation to ejaculate compared with genetically intact mice.\textsuperscript{48} It is presumed that in the absence of eNOS, NO antagonism of the sympathetic control of ejaculation is reduced, accounting for the overactive, sympathetically mediated ejaculatory response in these mice.\textsuperscript{49} There is evidence that NO plays a major role in seminal vesicle muscle contractions, as it was recently documented that these contractions can be inhibited \textit{in vitro} by NO donor drugs and PDE-5 inhibitors.\textsuperscript{50}

### Summary

- The ejaculatory phenomenon has been studied for over 200 years, and it continues to be an area of active research. There is a paucity of medications that provide both efficacy and lack of adverse effects for various ejaculatory conditions.

### REFERENCES

Endocrinology of male sexual function

Mario Maggi, Giovanni Corona, and Gianni Forti

Introduction

Male sexual activity consists of those physiological, anatomical, behavioral, and psychological functions that favor the union of male gamete to female gamete, thus ensuring continuation of the species. Although it is not essential for individual survival, it is pivotal for species survival, and, therefore, tightly controlled by two apparently distinct and autonomous systems: the nervous system and the endocrine system, which carry – by neural impulses (nervous system) or by chemical mediators (endocrine system) – sexual information from center to periphery and back. Nowadays, it is clear that these two systems constitute a co-ordinated network controlling, in an interlocking way, the entire cycle of the male sexual response, starting from the desire phase and ending in the orgasm phase. Separation between sexual hormones – substances that are secreted into the circulation and act as chemical effectors in other tissues – and sexual neurotransmitters – substances that are released from the nerve endings and act within the synapses – is no more than virtual. Oxytocin and α-melanocyte stimulating hormone are the best example. These two peptides act as hormones that stimulate, respectively, epididymal contractility and darkening of the skin, and as neurotransmitters within the hypothalamus, that co-ordinate sexual arousal and the corresponding behavior.1–3

This chapter describes the interaction between the ‘classic’ hormones and male sexual response, because the role of the nervous system is extensively covered elsewhere. It essentially deals with the effects of hormones (testosterone, prolactin, and thyroid hormones) that have proven action on at least some aspect of sexual behavior (sexual desire, sexual arousal, orgasm, and ejaculation), and it is mostly focused on results obtained in the human male, although results from animal studies will also be considered.

Testosterone

Testosterone production and activity

The testis is the key organ for male reproductive and sexual fitness. It secretes two main products, both essential for a successful mating strategy: testosterone, the main androgen produced by the Leydig cells, and mature germinal cells (sperm). Testosterone and sperm are produced in two distinct areas within the testis, the Leydig cells and the tubules, respectively, which are in continuous communication. Testicular activity is in fact regulated by intra-testicular factors (including testosterone) and by extra-testicular trophic factors produced by the pituitary, i.e. by the gonadotrophins luteinizing hormone (LH) and follicle stimulating hormone (FSH), which in turn are tightly regulated by the hypothalamic peptide gonadotropin-releasing hormone (GnRH). Circulating testosterone (T) binds with high affinity to a carrier protein, sex hormone binding globulin (SHBG), which also binds other sex steroids such as estrogens, although with lower affinity. The fraction of T unbound to SHBG is termed free T, and is thought to represent the bioactive fraction of total T. Measurement of free T represents the cornerstone of evaluating the androgen state. However, it is not an easy task, because the commercially available direct methods, based on a labeled T analog, are often unreliable, and separation of unbound T fraction at equilibrium dialysis is much too technically difficult. Therefore, at the present time the gold standard method for free T determination is the calculation of the free fraction,4 as derived from measurement of its total fraction and its carrier protein SHBG, according to a standard formula5 (available at http://www.issam.ch/freetesto.htm). In target tissues, T bioactivity can be further increased by its reduction to dihydrotestosterone (DHT) through two distinct 5α-reductase (5αR) isomers: 5αR type 1, which is androgen-independent, and 5αR type 2, which is more tightly androgen-controlled. In addition, T and its precursor, Δ4-androstenedione, can be actively transformed through P450 aromatase to other active metabolites: such as estrone and estradiol (E2). Hence, T exerts biological actions in part by itself, and in part through its reduction or aromatization to dihydrotestosterone (DHT) and estrogens, respectively. However, measurement of circulating DHT is often considered useless, because it does not reflect target tissue production of the hormone, while measurement of E2 in men is generally considered unreliable, because the available assays are designed for detecting the ovulatory peak in women.6 Figure 9.1 summarizes the major biological effect of testosterone.

The hypothalamus–pituitary–testis axis is maintained in a constant, tight equilibrium by the negative feedback of testicular products on the secretion of the hypothalamic hormone GnRH and gonadotropins from the pituitary gland. Testosterone and its active metabolites, DHT and estrogens, down-regulate GnRH and LH secretion, while the tubular product, mainly the inhibin family, exerts a parallel negative feedback
loop on FSH. Alteration of this axis results in male hypogonadism, defined as impaired testosterone secretion or activity and decreased sperm production.

**Male hypogonadism**

Male hypogonadism is usually categorized based on the site of dysfunction, as either:

- primary hypogonadism if the testis is dysfunctional and fails to release its products, although super-stimulated by the pituitary; or
- secondary hypogonadism if the testis is normal, but inadequately stimulated by gonadotropins.

Hence, the first type of hypogonadism is also defined as hypergonadotropic and the second one as hypogonadotropic. In addition, a hypogonadism-like syndrome can also derive from a reduced sensitivity (or insensitivity) to T and its metabolites (DHT and estrogens) or because of a reduced bioavailability of the hormone due to an increase in its carrier protein, SHBG. Finally, hypogonadism can be congenital or acquired later, during childhood or adult life. Table 9.1 summarizes the main causes of male hypogonadism divided according to the aforementioned criteria.

Interestingly, signs and symptoms of hypogonadism are quite similar irrespective of the site of origin of the disease. However, they differ greatly according to the age at onset of the hypogonadism. In other words, the phenotype of the hypogonadal patient is more often affected by the age of onset than by the site of origin (Figure 9.2). In very early-onset hypogonadism (VEOH) (i.e. starting during fetal life), symptoms may be dramatic, spanning from an almost complete female phenotype (as in Leydig cell hypoplasia type 2, complete androgen insensitivity, or absence of 17-β-hydroxysteroid dehydrogenase) to various defects in virilization – microopenis, hypospadias, cryptorchidism – (as in impaired secretion or activity of GnRH). In early-onset hypogonadism (EOH) (i.e. starting in the peri-pubertal period), because of milder central or peripheral defects (as in Klinefelter’s syndrome), there might be a delay in the onset of puberty with an overall eunuchoid phenotype, including scant body hair, high-pitched voice, and small testes, penis and prostate. In late-onset hypogonadism (LOH), symptoms are relatively mild and insidious and can be difficult to recognize and, therefore, to treat. In addition, in LOH, the site of origin of the problem is often unclear, because of mixed contributions of testicular and hypothalamus–pituitary failure. EOH and, in particular, VEOH are rather uncommon problems (although not rare, with prevalence ranging from one in 500 for Klinefelter’s syndrome to one in 100,000 for complete androgen insensitivity) and are more appropriately treated by dedicated specialists; on the other hand, LOH is a very common disorder but it often goes unrecognized by general practitioners.

**Hypogonadism and erectile dysfunction**

Sexual dysfunction can be considered the hallmark of hypogonadism, being present in all the forms, irrespective to the site of origin and the age of onset of the disease. In fact, in adult life, T is considered the hormonal fuel of sexual desire and also plays an important role in regulating other aspects of male sexual response, such as penile erection (both spontaneous and sexually induced) and frequency of intercourse and masturbation. A relationship between low T and delayed orgasm and low volume of ejaculates (T is the main trophic
Decreased testosterone production

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<td>GnRH mutations</td>
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<td>FSH-β and LH-β mutations</td>
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<tr>
<td>Pituitary aplasia or hypoplasia</td>
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<tr>
<td>Hemocromatosis</td>
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</tbody>
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| **Acquired**                                           |
| Pituitary tumors                                       |
| Functional and non-functional adenomas                 |
| Craniopharyngiomas                                     |
| Metastases                                             |
| Hematologic malignancy                                 |
| Rathke’s cyst                                          |
| Infiltrative                                           |
| Primary hypophysitis                                   |
| Sarcoidosis and tuberculosis, syphilis                 |
| Fungal, parasites, viral                               |
| Head trauma                                            |
| Empty sella                                            |
| Vascular                                               |
| Drugs                                                  |
| GnRH analogs (agonists and antagonists)                |
| Estrogens                                              |
| Anabolic steroids                                       |
| Progestogens (including cyproterone acetate)           |

<table>
<thead>
<tr>
<th>Testicular diseases (↑ gonadotrophins ± ↓ testosterone)</th>
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<tbody>
<tr>
<td><strong>Congenital</strong></td>
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<tr>
<td>Klinefelter syndrome</td>
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(Continued)
factor for both prostate and seminal vesicles) has also been reported. Figure 9.3 depicts the association between T levels and the aforementioned aspects of male sexuality in a large cohort of adult subjects consulting the outpatient clinic for sexual dysfunction at the University of Florence.

Although the association between T and spontaneous or nocturnal erections is supported by several studies, the relationship between T and sex-related erections is less apparent, or not at all documented. One possible explanation for this phenomenon derives from experimental studies. For penile erection, the most important pathway is the nonadrenergic–noncholinergic pathway, which, through the release of nitric oxide (NO), leads to an intracellular increase of cGMP, the main secondary messenger mediating tumescence in the penis. Interestingly, T affects both cGMP formation and degradation. In fact, beyond the well-known role of T in regulating NO formation, recent experimental evidence both in rodents and in humans showed that T also regulates the expression of phosphodiesterase (PDE) type 5, the hydrolytic enzyme involved in cGMP breakdown. This antithetical role of T seems to be the main way through which the peripheral hormonal regulation of penile erections occurs. Because T positively controls both the initiation of the erectile process (through NO synthase, NOS) and the end (through PDE-5), its net effect on erection might result as modest. Hence, erections are still possible in hypogonadal conditions, where decreased cGMP formation, caused by impaired NO production, may be counterbalanced by reduced PDE-5 activity and cGMP hydrolysis. The main physiological action of T is therefore to adjust the erectile process in a timely way as a function of sexual desire, thereby temporally aligning erections to sex. This is, most probably, the main reason why T controls the process of erection initiation (through NOS) and termination (through PDE-5). Accordingly, penile erection is not a random phenomenon but a discrete, temporally adjusted event, consequent to sexual desire and arousal.

A trophic effect of T on penile architecture has also been demonstrated in various animal species. In animal models, androgen deprivation by surgical and medical castration resulted in loss of trabecular smooth muscle and increase in

### Table 9.1 Continued

| Defects of testosterone biosynthesis (STAR, 20-22 desmolase, 3β-HSD, 17α-HSD, 17-20 desmolase, 17β-HSD) |
| Pure gonadal dysgenesis (46 XX and 46 XY) |
| Congenital anorchia |
| Leydig cell hypoplasia (including type I and II for LH–HCG receptor mutations) |
| Myotonic dystrophy (including type I and II) |
| Cryptorchidism (including INSL-3 and LGR-8 mutations) |
| Germinatal aplasia (Del Castillo syndrome, Sertoli-cell only syndrome) |
| Chromosome microdeletions |
| Autosomal translocations |
| FSHR mutations |
| Adrenoleukodystrophy |

**Acquired**

| Orchitis (including mumps and autoimmune disorders) |
| Chemotherapy |
| Alkylating agents |
| Methotrexate |
| Inhibitors of testosterone synthesis |
| Ketoconazole |
| Aminoglutethimide |
| Mitotane |
| Methyrapon |
| Testicular irradiation |
| Bilateral torsion |
| Varicocele |
| Bilateral trauma |
| General diseases (including renal failure, liver cirrhosis, diabetes mellitus) |

**Decreased testosterone bioactivity (↑ gonadotrophins, ↑ testosterone)**

**Congenital**

| Aromatase deficiency |
| 5α-reductase type II deficiency |
| Androgen receptor alterations |
| Complete androgen insensitivity syndromes |
| Partial androgen insensitivity syndromes |
| Kennedy syndrome and other extensions of CAG repeats |

**Acquired**

| Drug-induced androgen receptor blockade |
| Steroidal antiandrogen (cyproterone acetate, spironolactone) |
| Non-steroidal antiandrogen (flutamide, bicalutamide, nilutamide) |

| Drug-induced 5α-reductase activity blockade |
| Finasteride (type II) |
| Dutasteride (type I and II) |
| Drug-induced estrogen receptor blockade |
| Clomiphene, tamoxifen, raloxifene |
| Drug-induced aromatase activity blockade |
| Letrozole, anastrozole, exemestane |
| Increased sex hormone binding protein |
| Drug induced (antiepileptic, estrogen, thyroid hormones) |
| Hyperthyroidism |
| Liver diseases |
| Aging |
deposition of extracellular matrix, producing diffuse fibrosis and erectile dysfunction (ED). The androgen-dependent loss of erectile response is often restored by androgen administration. In addition, it has also been shown that T is involved in the maturation of penile tissue composition by promoting the commitment of pluripotent stem cells into the myogenic lineage and inhibiting their differentiation in the adipogenic lineage. Accumulation of adipocytes in the subtunical region of the corpus cavernosum might contribute to the impairment of the veno-occlusive mechanism. Hence, androgens are important for maintaining the contractile apparatus and for the formation and degradation of the main relaxing factor, cGMP.

**Figure 9.2** Characteristics of male hypogonadism, reported according to the age of onset of the disease and the patient’s phenotype. Schematic prevalence in male population is also shown. Size of ellipse reflects on the x-axis (logarithmic scale) age range of onset and on ordnates (logarithmic scale): incidence (right axis, logarithmic scale) and phenotype (left axis, arbitrary masculinization unit). VEOH, very early-onset hypogonadism – i.e. starting during fetal life for absence of testosterone formation or activity (e.g. Leydig cell hypoplasia type 2, complete androgen insensitivity or absence of 17β-hydroxysteroid dehydrogenase (yellow ellipse), or impaired secretion or activity of GnRH (red ellipse)); for causes see Table 9.1; EOH, early-onset hypogonadism – i.e. peri-pubertal onset, as in Klinefelter’s syndrome (blue ellipse); LOH, late-onset hypogonadism – i.e. in adulthood or aging (also termed andropause, gray ellipse). Adapted from Morelli et al. 7

**Hypogonadism and hypoactive sexual desire**

Human male sexual behavior is a multifaceted phenomenon – indeed, it can be profoundly affected by psychological, relational, social, and cultural factors in addition to the effect androgens. However, it is widely recognized that T is a clear determinant of sex drive and of the motivation to seek sexual contact. Several controlled and uncontrolled studies in hypogonadal men demonstrate an unequivocal role for T substitution in restoring sexual desire, spontaneous sexual thoughts, and attractiveness to erotic stimuli. It is less clear how and where T exerts these sex-activating effects in the human brain. Animal studies clearly indicate that sex steroid receptors are expressed in the central nervous system (CNS) and that T controls the activity of several neurotransmitters involved in sex-seeking behavior, such as dopamine. However, little information is available at present on mapping sex steroid receptors in the human CNS. Androgen receptors are present in distinct areas of the human brain, including the temporal, preoptic, hypothalamus, amygdala, midbrain, frontal, and prefrontal areas and the cingulate gyrus (Brodman area 24, BA24). BA24 is part of the limbic cortex deeply involved in balancing emotional behavior and generalized arousal reaction; it has been found in two studies to be activated by explicitly erotic films by using positron emission tomography or functional magnetic resonance imaging. Interestingly, T supplementation to hypogonadal men with several symptoms, including lack of libido, increased blood perfusion (assessed by single-photon emission computed tomography) in BA24, in the midbrain, and in the superior frontal gyrus (BA8), as well as reducing hypogonadal symptoms. Stoleru and colleagues previously identified another androgen-sensitive brain area by describing a clear positive association between circulating T plasma levels and BA37 (the middle occipital gyrus) during exposure to erotic movies, whereas during neutral exposure the relationship was still significant, but with a negative relationship. Activation of BA37 by visual sexual stimulation was confirmed in a further study, and related to processing novel visual stimuli. Hence, several cerebral areas closely linked to sexual drive are androgen-sensitive. However, it should be noted that sexual desire or motivation is different from, although closely related to, sexual arousal. The latter refers to the cognitive and emotional component responsible for bringing males to the threshold for initiating copulation (feeling sexually excited) and includes penile erection. Most of the functional brain imaging studies in humans mentioned so far referred more to sexual arousal (and erection) than to sexual motivation. The interaction between androgen level and sexual behavior is further complicated by the fact that they are mutually dependent and can therefore feedback iteratively. In fact, not
only can T affect sexual activity, but sexual behavior also positively affects T production. An often-cited, single-subject observation published almost 40 years ago in *Nature* opened up this second scenario. An island resident observed an increase in beard growth on the day preceding and also during his occasional visits to his mainland lover. During the following years only scanty reports substantiated this anecdotal report, demonstrating a rise in T during sexual intercourse or exposure to erotic movies. Conversely, other reports addressing the question of a sexual activity-induced rise in T plasma levels were negative. However, Stoleru and colleagues, sampling male volunteers every 10 minutes for 12 hours, found an increased pulsatile release of LH, with a consequent increase in T, occurring soon after exposure to erotic movies but not to neutral movies. In line with this finding, in the past few years Jannini and colleagues have produced compelling evidence that has robustly substantiated the hypothesis of an LH-mediated, sex-induced drive in T production.

In conclusion, T tightly regulates penile responsiveness to sexual stimuli, controlling both the initial and final steps of erections and synchronizing them to sexual desire, which is clearly under androgen regulation. This might explain why, even in absence of T, there are penile erections (as in children and eunuchs), which are, however, not often finalized to sexual intercourse, because of the blunted sexual motivation.

### Prolactin

Prolactin (PRL) is a 23 kDa polypeptide secreted by lactotropha cells of the anterior pituitary. As well as the usually predominant monomer, circulating forms of PRL include high-molecular-weight forms such as macroprolactin (>100 kDa), a biologically inactive complex of PRL and immunoglobulin G. PRL is unique among anterior pituitary hormones in that it is under tonic hypothalamic inhibition via dopamine (D2 receptors) produced by tubero-infundibular neurons. Hormonal factors facilitating prolactin secretion or production include estrogens, thyrotropin-releasing hormone (TRH), which also stimulates production of thyrotropin (thyroid stimulating hormone, TSH), serotonin, and endogenous opiates.

In contrast to the clear function of PRL in female reproduction (i.e. promoting breast feeding), the physiological

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**Figure 9.3** Testosterone plasma levels in 2218 patients afferent to the Andrology Unit for Sexual Disorders at the University of Florence. Parameters in abscissa are derived from SIEDY structured interview and its Appendix A. (a) Hypoactive sexual desire. No, the patient’s desire is unmodified or increased; mild, desire is moderately reduced in <50% of potential occasions; moderate; desire is reduced in >50% of potential occasions; severe, the patient has had no desire to make love. (b) Lack of sex-related erections. No, <25% of cases; mild, 25–50% of cases; moderate, 51–75%; severe, >75%. (c) Lack of nocturnal erections. No.; the patient reports spontaneous nocturnal or morning erections, with the same frequency previously observed; mild, nocturnal or morning erections are present, but their frequency is somewhat lower than that observed previously; moderate, the frequency of nocturnal or morning is reduced by at least 50%; severe, no nocturnal or morning erections are present. (d) Number of episodes of sexual intercourse per month. (e) Number of episodes of masturbation per month TT, total testosterone. *p<0.01, **p<0.005; ***p<0.0001 vs the first point. Taken from Morelli et al., 2007, Traish et al. and from unpublished observations.
Table 9.2 Etiology of male hyperprolactinemia. An increase in prolactin may derive from an abnormal detection of biologically inert high-molecular-weight form of prolactin (pseudo-hyperprolactinemia) or from physiological or pathological conditions.

<table>
<thead>
<tr>
<th>Physiologic</th>
<th>Pathologic</th>
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<tr>
<td>Stress (including venepuncture)</td>
<td>Hypothalamic–pituitary stalk damage</td>
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<td>Sleep</td>
<td>Hypothalamic tumors</td>
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<td>Orgasm</td>
<td>Germinomas and other germ tumors</td>
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<td>Exercise</td>
<td>Astrocytomas</td>
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<td>Breast nipple or areola stimulation</td>
<td>Craniopharyngiomas</td>
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<td>Meningioma</td>
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<td>Metastases</td>
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<td>Infiltrative and infective disorders</td>
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<td>Langerhans’ histiocytosis</td>
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<td>Sarcoïdosis and tuberculosis, syphilis</td>
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<td>Encephalitis</td>
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<td>Head trauma</td>
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<td></td>
<td>Pituitary diseases</td>
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<td>Pituitary tumors</td>
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<td>Prolactinoma</td>
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<td>Acromegaly</td>
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<td>Plurihormonal adenoma</td>
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<td>Macroadenoma with stalk compression</td>
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<td>Infiltrative</td>
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<td>Primary hypophysitis</td>
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<td>Sarcoïdosis and tuberculosis, syphilis</td>
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<td>Fungal, parasites, viral</td>
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<td>Empty sella</td>
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<td>X-irradiation</td>
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<td>Systemic disorders</td>
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<td>Chronic renal failure</td>
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<td>Hypothyroidism</td>
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<td>Epileptic seizures</td>
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<td>Herpes zoster</td>
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Table 9.2 Continued

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<tr>
<th>Drug induced</th>
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<tr>
<td>Antipsychotics and other dopamine receptor blockers (including antiemetic)</td>
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<tr>
<td>Phenothiazines (chlorpromazine, mesoridazine, thiordazine, fluphenazine, perphenazine, trifluoperazine)</td>
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<tr>
<td>Butyrophenones (haloperidol, pimozide, fluspirilene, penluridil, risperidone)</td>
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<tr>
<td>Benzamides (sulpiride, amisulpride, levosulpiride, cisapride, metoclopramide)</td>
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<tr>
<td>Thioxanthenes (chlorprothixene, thiothixene)</td>
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<tr>
<td>Dopamine synthesis inhibitors</td>
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<td>α-Methyl dopa</td>
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<tr>
<td>Catecholamine depleters</td>
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<tr>
<td>Reserpine</td>
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<tr>
<td>Antidepressants</td>
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<tr>
<td>Selective serotoninergic reuptake inhibitors (citalopram, paroxetine, sertraline, fluoxetine, fluvoxamine, escitalopram)</td>
</tr>
<tr>
<td>Serotonergic–noradrenergic reuptake inhibitor and atypical antidepressants (venlafaxine, trazodone, mirtazapine, bupropion)</td>
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<tr>
<td>Tricyclics (chlorimipramine, amitriptyline)</td>
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<tr>
<td>Opiates</td>
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<td>H₂ antagonist</td>
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<td>Cimetidine</td>
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<td>Ranitidine</td>
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<td>Calcium-channel blockers</td>
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<td>Verapamil</td>
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<td>Hormones</td>
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<tr>
<td>Estrogens</td>
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<tr>
<td>Antiandrogens</td>
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<tr>
<td>Anticonvulsants</td>
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<td>Phenytoin</td>
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**Figure 9.4** Age-adjusted odd ratio (OR) for different parameters associated with mild hyperprolactinemia (prolactin [PRL] levels >420 mU/liter [20 ng/ml], closed diamonds) or severe hyperprolactinemia (PRL levels >735 mU/liter [30 ng/ml], open diamonds). SSRI, selective serotoninergic reuptake inhibitor; SNRI/atypical, serotoninergic–noradrenergic reuptake inhibitor atypical antidepressants; hypoactive sexual desire, moderate to severe hypoactive sexual desire as assessed by SIEDY structured interview score (question number 14: ‘In the past 3 months, did you have more or less desire to make love?’; rating 0, no; rating 1, mild reduction; rating 2, moderate reduction; rating 3, severe reduction). Positive pituitary magnetic resonance imagine (MRI), detection of abnormality in sellar or parasellar regions on MRI. Hypothyroidism (TSH >4 mU/liter). Severe hypogonadism: total testosterone <8 nmol/L.

In addition, SHPRL is a medical problem that must be recognized and treated, not only because a sellar or parasellar tumor might be detected by pituitary imaging (see Figure 9.4), but also because removing the underlying disorder will restore sexual activity. Although SHPRL is usually associated with secondary hypogonadism, due to a PRL-dependent decrease in LH secretion (see Figure 9.4), PRL seems to play a direct role in the control of male sexual desire through central dopamine metabolism. Accordingly, in hyperprolactinemic subjects, testosterone treatment was not able to restore libido, while prolactin-lowering drugs were very effective both in raising testosterone levels and sexual desire.

In conclusion, MHPRL has modest or undetectable effects on male sexual behavior, and is often the result of medications or venipuncture stress. In contrast, SHPRL, severely compromising sexual desire, almost always causes sexual dysfunction.

**Thyroid hormones**

The thyroid gland produces, under TSH control, two major active hormones, thyroxine (T₄) and tri-iodothyronine (T₃), which circulate in human blood tightly bound to carrier proteins, including thyroxine binding globulin. Free fractions of thyroid hormones are the biologically active hormones (FT₁ and FT₃), which regulate protein, fat, and carbohydrate metabolism. Hence, all organs and tissues are at least partially...
affected by thyroid diseases. For instance, both hypothyroidism and hyperthyroidism result in clear alterations in the cardiovascular and mental state. However, the association between thyroid diseases and sexual dysfunction in men has not been systematically studied until recently. In a consecutive series of 755 men presenting with sexual dysfunction, a two-fold greater prevalence of hyperthyroidism was evident among the men with premature ejaculation. This figure is confirmed in a larger sample (of 1854 men), showing that subclinical or overt hyperthyroidism (TSH <0.2 mU/L, with normal or elevated FT3, and FT4) was present in less than 1% of those not complaining of premature ejaculation, while it was present in 2.3% of those with premature ejaculation (Figure 9.5).

Similarly, Carani and colleagues, in a small multicenter, prospective study, demonstrated that 50% of hyperthyroid patients have premature ejaculation, a prevalence that was substantially reduced (15%) by treating the underlying disease, with a consequent doubling of ejaculatory latency. In the same study it was shown that medical treatment of the opposite state, hypothyroidism, resulted in a two-fold decrease in ejaculatory latency and a reduction in delayed ejaculation. Hence, the view that thyroid hormones regulate the ejaculatory reflex is emerging. The study by Carani and colleagues also suggests that low sexual desire and ED might be due to hypothyroidism and can be treated by normalizing thyroid hormones. The underlying pathogenic mechanisms are not completely understood. Although it is possible that a hyperthyroidism-induced PRL rise could mediate these negative effects on male sexuality (see Figure 9.4), a direct role for thyroid hormones on reproductive tissues has also been postulated. More studies are needed to clarify the role of thyroid hormones.

In conclusion, thyroid disease could underlie some form of sexual dysfunction in the male. Measurement of TSH (and possibly FT3 and FT4) is encouraged in subjects who present with premature ejaculation.

REFERENCES


10 Pathophysiology of erectile dysfunction: molecular basis

Biljana Musicki and Arthur L Burnett

Introduction

The pathophysiology of erectile function refers to derangement of the normal erectile response and, as a scientific field, implies investigation of biological factors and underlying molecular mechanisms associated with these derangements. This area of scientific knowledge has been built on clinical observations and experimental studies. Clinically, various disease states and risk factors, such as diabetes, hypertension, atherosclerosis, and cardiovascular diseases, have been associated with erectile dysfunction (ED). Experimental studies have been carried out to elucidate specific derangements and specific mechanisms associated with the disturbances that underlie ED.

It may be helpful to consider the causes, conditions, and molecular mechanisms of ED in the context of the normal erectile response. Penile erection is a complex neurovascular process involving relaxation of the corpus cavernosal smooth muscle combined with increased arterial inflow into the penis and restricted venous outflow from the penis. The process relies on a co-ordination of the nervous system, including the hypothalamus, the spinal cord, and peripheral nerve distributions to the penis. It is also influenced by hormonal substances acting within the penis. Co-ordination extends to cellular components of the penile vascular response, such as endothelial cells, smooth muscle cells, and locally released biochemical factors. Defective regulation of penile erection can be associated with alteration in any of these components (Figure 10.1).

Current knowledge supports particular mechanisms of vascular biology in the penis as fundamental properties of erection physiology. The balance between vasorelaxation and vasoconstriction determines penile flaccidity versus erection. Relaxation of the corporal smooth muscle is the key determinant of the erectile response. It permits engorgement of the corpora cavernosa with blood. Compression of the dilated blood vessels against the rigid tunica albuginea restricts venous drainage (veno-occlusion), allowing penile rigidity. The achievement of normal veno-occlusion is primarily determined by the content of functional corporal smooth muscle and by structural integrity of the erectile tissue.1,2 Thus, factors that impede vasorelaxation or promote vasoconstriction would be considered effectors of ED pathophysiology. Similarly, factors that disrupt veno-occlusion would also be considered effectors of ED pathophysiology.

Major scientific advances have occurred in the study of erection physiology at the molecular level. Specific signaling pathways have been described that provide a molecular biological basis for penile erection. Our current understanding is that penile erection is mainly mediated by the nitric oxide (NO) pathway.3,4 NO is synthesized by neuronal nitric oxide synthase (nNOS), expressed in autonomic nerve endings, and by endothelial nitric oxide synthase (eNOS), expressed in vascular and sinusoidal endothelium of the penis. Neuronally derived NO initiates penile erection, while endothelial NO maintains erection.5 Accordingly, the common factors contributing to ED include reduced activity of nNOS and eNOS and decreased NO bioavailability (Figure 10.2). cGMP and cAMP are primary intracellular mediators of corporal smooth muscle relaxation.5,6 Opposing this activity, the RhoA–Rho-kinase signaling pathway is the main mediator of cavernosal tissue contraction.6,7 Derangements of these mechanisms probably explain the pathophysiology of ED associated with different disease states.

In this chapter we present current knowledge of the pathophysiology of ED. Our intent is to describe two major categories of the erection paradigm, vasculogenic and neurogenic, but consider these in reference to ED. Hormonal influences on ED are handled elsewhere in the book. After describing these two major categories, we proceed with a description of major disease states associated with ED, detailing molecular mechanisms associated with each disease state.

Vasculogenic erectile dysfunction

Accumulating evidence indicates that ED is predominantly a vascular disease. Vasculogenic ED may be due to arterial or to cavernosal dysfunction (veno-occlusive), resulting in reduced blood inflow into the penis, or excessive blood outflow from the penis. Vasculogenic ED refers to the derangements in the function and structure of endothelial and smooth muscle cells in the penis. The inability of the endothelium to produce vasorelaxing messengers, increased vasoconstriction, and reduced endothelium-dependent vasodilatory response of smooth muscle cells are all sources for the development of endothelial dysfunction in the penis and for vasculogenic ED. eNOS-mediated and NO-independent vasorelaxation are downregulated in various diseases states. Smooth muscle signaling is affected by upregulation of the vasoconstricting pathways and
Figure 10.1 Common medical conditions associated with ED and their putative levels of effect based on the neuroaxis of penile erection. The regulation of penile erection involves the co-ordination of the nervous system (i.e. brain, spinal cord, and peripheral nerves) and the vascular circulation of the penis.

Figure 10.2 NO-mediated penile erection. NO is synthesized from its precursor L-arginine by nNOS and eNOS, primarily localized in autonomic nerve endings and endothelial cells of the penis, respectively. In response to psychogenic and reflexogenic neuronal impulses, activation of nNOS initiates penile erection. Blood-flow-related mechanisms facilitate and maintain maximal erection by phosphorylation and activation of eNOS. NO diffuses to adjacent smooth muscle cells where it activates soluble guanylyl cyclase (sGC) and increases the production of 3'-5'-cyclic guanosine monophosphate (cGMP) from 5'-guanosine triphosphate (GTP). Subsequent activation of cGMP-specific protein kinase I (cGKI) reduces contractile activity and promotes relaxation of smooth muscle cells and erection. Degradation of cGMP in the penis to inactive 5'-GMP, which terminates NO signaling and returns the penis to the flaccid state, is catalyzed primarily by PDE-5.

Impaired growth factor and cytokine signaling (Figure 10.3). Increases in oxidative stress, which refers to the imbalance between the production and elimination of reactive oxygen species (ROS),a affect normal penile erection and are featured in the development of vasculogenic ED. Endothelial dysfunction is an early stage of vascular damage, which can lead to more severe changes, such as atherosclerosis in the systemic vasculature, and it manifests itself clinically as coronary, renal, cerebral, and peripheral artery disease. In fact, vascular ED appears to be one of the earliest signs of systemic microvascular and macrovascular diseases and may be considered an early marker for cardiovascular disease.10

The following section represents a sub-categorization of major vasculogenic molecular mechanisms involved in normal erectile function. This framework can be applied to facilitate understanding of mechanisms of vasculogenic ED.

Endothelial nitric oxide synthase
In normal endothelial function, NO has vasodilatory properties and counterbalances RhoA–Rho-kinase-mediated vasoconstriction, thus regulating vascular tissue homeostasis. Conversely, in pathologic conditions, eNOS uncoupling and formation of peroxynitrite from the reaction of NO with superoxide anion results in pro-oxidant effects of NO. The balance between NO bioavailability, vasoconstrictor function, and vascular generation of ROS is crucial for maintaining normal erectile ability. eNOS is regulated transcriptionally and post-translationally.11 The latter mechanisms involve calcium–calmodulin binding, fatty acid modification, alterations in intracellular translocation, substrate and cofactor availability, dimerization of the enzyme subunits, binding to other proteins, and phosphorylation. Phosphorylation of eNOS at Ser-1177 by shear stress and vascular endothelial growth factor (VEGF) increases the enzyme’s activity, while phosphorylation of eNOS at Thr-495 decreases the enzyme’s activity. Interaction of eNOS with heat-shock protein (Hsp) 90 positively regulates the enzyme’s activity, whereas interaction of eNOS with caveolin-1 negatively regulates the enzyme’s activity.12 Derangements in any of the molecular pathways that regulate eNOS may induce vasculogenic ED.

Nitric oxide-independent endothelium-derived relaxing factors
Endothelial cells release other vasodilators besides NO, including prostacyclin and endothelium-derived hyperpolarizing...
factor (EDHF). Prostacyclin, synthesized by both the endothelium and smooth muscle, is involved in cAMP-mediated smooth muscle relaxation. Endothelium-dependent vasodilation in smaller arteries and arterioles is mostly attributed to non-NO, non-prostacyclin-induced hyperpolarization mediated by EDHF. There is considerable controversy regarding the identity and the mechanism of action of EDHF. It is thought that the hyperpolarization of smooth muscle cell membrane by EDHF predominantly involves activation of calcium-dependent potassium channels. While the exact role and mechanism of their action remain to be fully elucidated, decreased production or action of NO-independent vasoconstrictor factors in the penis may contribute to vasculogenic ED.

**Smooth muscle mediators**

The degree of contraction of the corpus cavernosum smooth muscle and the functional state of the penis is determined by the balance between pro-erectile and anti-erectile (vasoconstrictive) mechanisms, which operate physiologically in the penis. Vasoconstriction is evoked by norepinephrine through alpha-adrenergic receptors, endothelins, angiotensins, and thromboxane A₂. Agonist-induced activation of G protein-coupled receptors increases influx of extracellular calcium and increases phospholipase C (PLC) activity. PLC cleaves membrane-bound phosphatidylinositol into inositol triphosphate and diacylglycerol, resulting in an elevation of intracellular calcium concentrations. During this phase, calcium-calmodulin activates myosin light chain kinase, leading to increased phosphorylation of myosin light chain, acting on myosin assembly, and initiation of smooth muscle contraction. Increased production of vasoconstrictors may decrease vasodilation and result in ED.

**RhoA–Rho-kinase pathway**

While smooth muscle contraction is regulated primarily by cytosolic calcium, once the calcium levels return to basal levels, the calcium-independent increase in vascular smooth muscle tone, known as calcium-sensitization, takes over. This pathway involves RhoA and its downstream effector Rho-kinase. Activated Rho-kinase phosphorylates myosin light chain phosphatase and thereby inhibits its activity, resulting in enhanced contractile response at low calcium levels (Figure 10.4). Upregulated function or activity of the RhoA–Rho-kinase pathway may increase smooth muscle contractility and result in ED.

**Reactive oxygen species**

ROS may affect eNOS activity, endothelial NO availability, smooth muscle cell integrity, and RhoA–Rho-kinase pathway function. Superoxide anion is produced in a variety of cells, including vascular smooth muscle cells and endothelial cells. Many other ROS are formed secondary to reactions involving superoxide. Potential sources of superoxide anion include nicotinamide adenine dinucleotide phosphate [NAD(P)H] oxidase, uncoupled eNOS, xanthine oxidase, peroxisomal oxidases, cyclo-oxygenases, and mitochondrial electron transport. Superoxide anion may directly inactivate NO and decrease its bioavailability. Moreover, the reaction of superoxide anion and NO results in the formation of reactive nitrogen species such as the highly toxic molecule peroxynitrite. Peroxynitrite may cause oxidative damage to DNA, proteins and lipids, uncouple eNOS, promote release of vasoconstrictors, increase apoptosis, and cause tissue injury and inflammation. Enzymes that degrade ROS, such as superoxide dismutase, catalase, and glutathione peroxidase, play an important role in the cellular protection against ROS. Increased oxidative stress has been implicated in the pathophysiology of ED (Figure 10.5).

**Growth factors and cytokines**

Growth factors act as paracrine and autocrine regulators in the vasculature. Vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF), and its binding proteins, basic fibroblast growth factor (bFGF), and transforming growth factor (TGF)-beta-1 have been characterized in the penis. VEGF is an angiogenic factor that directly activates eNOS and regulates apoptosis. IGF-1 has been implicated in the regulation of vascular smooth muscle proliferation and migration, and it plays a role in the control of cell growth, cell survival, and mitogenesis. The cytokine TGF-beta-1 promotes the synthesis of collagen and inhibits growth of vascular smooth muscle cells. Impaired production of growth factors and cytokines and their impaired signaling in the penis accordingly may impact the function and structure of endothelial and cavernosal smooth muscle cells.

**Neurogenic erectile dysfunction**

Neurogenic ED results from any defect in neurotransmission to the smooth muscle of the penis. It can be related to trauma.
Oxidative–nitrosative stress

**Cell type**
- Endothelial cells
- Smooth muscle cells
- Nerve cells

**Mechanism**
- eNOS uncoupling, protein interaction subcellular localization, phosphorylation
- NO-independent factors
- RhoA–Rho-kinase
- Ion channels (Potassium channels)
- nNOS uncoupling (?), protein interaction, subcellular localization, phosphorylation (?)
- Inducible NOS
- PARP

**Effect**
- Decreased vasorelaxation
- Endothelial cell loss
- Increased vasoconstriction
- Fibrosis
- Altered neurotransmission
- Neurodegeneration

Figure 10.5 Proposed model of oxidative–nitrosative stress in ED. Several ROS, such as superoxide anion, hydrogen peroxide, hypochlorous acid, hydroxyl radical, reactive aldehydes, lipid peroxides, and peroxynitrite, are believed to mediate cellular degeneration in vasculogenic and neurogenic ED states. Peroxynitrite formation resulting from the direct interaction between superoxide ion and an excess of NO (such as inducible NOS-generated NO) is referred to as nitrosative stress. ROS may attack proteins, lipids, and nucleic acids, and they may further generate ROS and potentiate oxidative–nitrosative stress. ROS may produce a number of pathological effects at all cellular levels involved in penile erection. Some of the effects are unique for different cell types, while some other effects may be common among different cell types. Numerous effectors and signaling mechanisms are targets for ROS, such as guanylyl cyclase, phospholipases, phosphatases and protein kinases, ion channels, gene expression and production of growth factors, stress response elements, and apoptosis pathways. All NOS isoforms are subject to ‘uncoupling’ by ROS as a result of oxidation of the zinc thiolate cluster of the enzyme and the cofactor tetrahydrobiopterin, and the decreased availability of the NOS substrate L-arginine, destabilizing the NOS dimer and resulting in the increased production of ROS and reduced NO production by the enzyme. ROS may activate numerous transcriptional factors such as nuclear factor-kappa-B (NF-kB), hypoxia-inducible factor-1-alpha (HIF-1-alpha), and activator protein-1 (AP-1). Activation of poly (ADP-ribose) polymerase (PARP) in response to ROS-mediated DNA strand breaks depletes intracellular energy reserves and causes necrotic cell death. Similarly, changes in anti-apoptotic markers, such as phosphorylated protein kinase B (Akt), B-cell CLL/lymphoma 2 (Bcl-2) and phosphorylated BCL2-antagonist of cell death (Bad), and pro-apoptotic markers, such as active caspase-3 and BCL2-associated X protein (Bax), may result in apoptosis affecting different cell types. ROS may also affect the production and action of growth factors and cytokines involved in erection. In endothelial cells, ROS may affect ENOS-dependent and NO-independent vasorelaxing factors, resulting in decreased vasorelaxation and endothelial cell loss. In smooth muscle cells, ROS can affect vascular reactivity via direct action on receptors, ion channels (for potassium, calcium, sodium, and chloride) or via specific signaling pathways, such as activation of the RhoA–Rho-kinase pathway, resulting in increased vasoconstriction and tissue fibrosis. Neuronal cell death may occur as a result of PARP activation and increased apoptosis, resulting in altered neurotransmission and neurodegeneration. Many other, still not fully explained, mechanisms may also be involved in oxidative–nitrosative stress-induced ED.

Neuronal nitric oxide synthase
Nitricergic neurotransmission refers to neuronal NO signaling in penile erection. The nitricergic activation of penile erection involves discrete brain regions such as the medial preoptic area (MPOA)29,30 and the paraventricular nucleus (PVN)31–33 within the hypothalamus where the erectile stimuli originate, the L6–S1 region of the spinal cord, and the peripheral nerves of the corpora cavernosa.34 Accordingly, any disease state involving disturbances in nitricergic transmission represents a neurologic basis of ED.

nNOS activity is regulated at the transcriptional level and by multi-site phosphorylation, protein–protein interactions, and subcellular localization mechanisms.35–38 Psychogenic and tactile (reflexogenic) stimuli initiate penile erection through the activation of nNOS. This is achieved mainly by

to nerves, such as occurs in spinal cord injury; it can occur after injury of nerves as a consequence of surgeries for cancer of the prostate, bladder and colon; and it can be an associated element of a neurological disease such as multiple sclerosis. More commonly, neurogenic ED results from the degeneration and loss of the nerves associated with non-traumatic chronic diseases such as diabetes. Although the molecular mechanisms underlying neurogenic ED are not well understood, the principal theories include impairment in nNOS function and NO bioavailability, reduced blood supply to nerve tissue, deficiency of neurohormonal growth factors, and increased oxidative stress.28

The following section represents a sub-categorization of major neurogenic molecular mechanisms involved in normal erectile function. This framework can be applied to facilitate understanding of mechanisms of neurogenic ED.
depolarization-induced calcium entry and calcium binding to calmodulin by means of calcium flux through the N-methyl-D-aspartate receptor (NMDAR). Both the NMDAR and inhibitors of nNOS activity, such as protein inhibitor of NOS (PIN) and the carboxyterminal PDZ ligand of nNOS (CAPON), are expressed in pelvic ganglia and penile nerves (in the case of PIN, NMDAR, CAPON)\(^\text{60,61}\) and in the hypothalamic and spinal cord regions involved in penile erection (in the case of PIN).\(^\text{62}\) Derangement of nNOS expression and nNOS activity, including its interaction with its modulators, may compromise nitricergic control of erection.

**Other neurotransmitters**

A host of neurotransmitters besides NO are involved in penile erection. At the levels of brain and spinal cord they include facilitatory neurotransmitters of penile erection (such as dopamine, acetylcholine, oxytocin, and adrenocorticotropic–alpha-melanocyte-stimulating hormone), or inhibitory neurotransmitters (such as gamma aminobutyric acid (GABA), serotonin, and opioid peptides).\(^\text{33–47}\) It is possible that defective neurotransmission involving such neurochemicals contributes to neurogenic ED.

**Growth factors and neurotrophic factors**

Many paracrine and autocrine factors can modulate the erectile response by affecting neuronal development and neuron regeneration. They include classic neurotrophins (such as nerve growth factor (NGF)),\(^\text{48}\) brain-derived neurotrophic factor (BDNF),\(^\text{49,50}\) neurotrophin-3 (NT-3), and neurotrophin-4 (NT-4); growth factors (fibroblast growth factor, VEGF, IGF-1 and IGF binding protein-3);\(^\text{52,53}\) immunophilin ligands,\(^\text{54–58}\) and atypical neurotrophic factors (such as growth hormones,\(^\text{59}\) the glial cell derived neururtin,\(^\text{60}\) the morphogenic sonic hedgehog protein,\(^\text{61}\) and erythropoietin).\(^\text{62}\) Impairment in the production and action of these factors may compromise penile erection.

**Reactive oxygen species**

As with endothelial-dependent vasorelaxation, nitricergic neurotransmission may be affected by oxidative stress. The brain has relatively low levels of antioxidant defenses and a high lipid content, which is highly susceptible to ROS attack.\(^\text{63}\) Increases in oxidative stress may initiate apoptosis in nitricergic nerves, affect nNOS dimerization, and reduce NOS cofactor availability.

**Aging**

ED is highly associated with aging. Age-related ED is due to vasculogenic and neurogenic factors. The vasculogenic component of age-related ED includes disturbances at the level of both endothelial and smooth muscle cells of the penis and its vascular supply. At the endothelial level, decreased NO-mediated vasorelaxation has been attributed to impaired eNOS expression (decreased or increased),\(^\text{64–68}\) decreased eNOS activity and phosphorylation,\(^\text{64}\) decreased content of the NOS substrate, L-arginine,\(^\text{62,69,70}\) reduced activation of protein kinase G-1 by cGMP,\(^\text{71}\) and excessive cGMP degradation by upregulated PDE-5.\(^\text{72}\) Increased phosphorylation of eNOS at Thr-495, a negative eNOS regulatory site, prevents eNOS phosphorylation at Ser-1177, a positive eNOS regulatory site, and prevents eNOS activation in the penis by shear stress, a physiological eNOS stimulator in the vasculature.\(^\text{64}\) At the smooth muscle cell level, vasoconstriction is increased mainly through an upregulation of endothelin and RhoA–Rho-kinase activation.\(^\text{72–74}\)

Cavernosal smooth muscle cells progressively degenerate, owing to increased apoptosis and impaired growth factor and cytokine signaling in the penis. Enhanced apoptotic and decreased anti-apoptotic activities have been demonstrated in the corpora cavernosa of aged animals.\(^\text{75,76}\) The production of VEGF\(^\text{64}\) and IGF-1 is decreased, while TGF-beta-1 production is increased\(^\text{77}\) in the penis of aged animals. The molecular explanation for the stimulatory effects of VEGF on penile erection is preservation of eNOS function via phosphorylation\(^\text{64}\) and preservation of corporal smooth muscle integrity through the inhibition of apoptosis.\(^\text{78}\) Increased production of the cytokine TGF-beta-1 promotes the synthesis of collagen, inhibits growth of vascular smooth muscle cells, and causes tissue fibrosis.\(^\text{77}\) Apoptosis and degeneration of smooth muscles, increase in connective tissue, and fibrosis in the penis all lead to corporal veno-occlusive dysfunction and ED.\(^\text{75,79}\)

Molecular mechanisms underlying decreased neurogenic-mediated corpus cavernosum relaxation associated with aging involve disturbances in the central and peripheral systems of neurotransmission. Central neuropathy involves increased apoptosis in the hypothalamic PVN and MPOA.\(^\text{80}\) Neuronal loss in the brain has been attributed to an increase in the rate of apoptosis by oxidative and nitrosative stress. The hypothalamic PVN and MPOA of aged rats exhibit increased expression of inducible NOS,\(^\text{80}\) which may lead to excessive production of NO and consequently of peroxynitrite. Peripheral mechanisms have been attributed to a reduction in nitricergic penile nerve fibers in the penis and decreased nNOS expression and activity,\(^\text{81,83}\) resulting in insufficient production of NO at the penile nerve terminals in response to sexual stimulation. Inadequate nNOS activation in the penis of aged rats may be restored by inhibition of PIN, implying a role for this endogenous NOS inhibitor in the pathophysiology of age-associated neurogenic ED.\(^\text{84}\)

**Diabetes mellitus**

Diabetes mellitus is one of the major risk factors for ED. It has been estimated that 50–75% of diabetic men have ED.\(^\text{85}\) Multiple mechanisms involving vasculogenic and neurogenic factors are involved in ED associated with diabetes. Nutrition, endocrine disorders, and anti-diabetic drugs have also been implicated in the etiology of diabetic ED.\(^\text{86}\) Molecular mechanisms involving oxidative stress may be common to both vasculopathy and neuropathy in the diabetic penis.

Metabolic disorders associated with diabetes include hyperglycemia, excess free fatty acids, and insulin resistance. Hyperglycemia is a fundamental metabolic insult in diabetes. Hyperglycemia-induced oxidative stress may trigger several
Pathophysiology of erectile dysfunction: molecular basis

Hypercholesterolemia

Hypercholesterolemia resulting in atherosclerosis of the penile vasculature is one of the leading causes of ED. ED has been attributed to both vasculogenic and neurogenic factors, although the molecular mechanisms of the latter are largely unknown.

Decreased NO signaling and increased oxidative stress have been postulated to be major molecular factors contributing to hypercholesterolemia-induced ED. Reduced NO signaling in the penis occurs by several mechanisms:

- reduction in eNOS expression;\textsuperscript{125,126}
- reduction in eNOS activity caused by decreased content of L-arginine;\textsuperscript{127} decreased eNOS phosphorylation at Ser-1177,\textsuperscript{125,126,128,129} increased caveolin-1 expression\textsuperscript{130} and its interaction with eNOS (Musicki and Burnett, unpublished data), which negatively regulates eNOS, and increased eNOS uncoupling (Musicki and Burnett, unpublished data); and
- deranged cGMP signal transduction pathways.\textsuperscript{131}

Endothelium-independent relaxation\textsuperscript{132,133} of the corpus cavernosum is also decreased. Oxidative modification of low-density lipoprotein (LDL), the major carrier of plasma cholesterol, plays a crucial role in the development of hypercholesterolemia-associated atherosclerosis. LDL can undergo oxidative modification by superoxide and peroxynitrite, and it accumulates in atherosclerotic plaques. Corpus cavernosal tissue of cholesterol-fed animals exhibits increased production of superoxide anion,\textsuperscript{131,134} caused by activated NAD(P)H oxidase\textsuperscript{131} and uncoupled eNOS (Musicki and Burnett, unpublished data). eNOS uncoupling is not only associated with increased superoxide anion formation, which reacts with NO, thereby further generating peroxynitrite, but also with reduced NO production, because the electron flux is shifted from L-arginine to molecular oxygen.\textsuperscript{135}

Vasoconstriction is increased through an upregulation of cavernosal Rho-kinase activity.\textsuperscript{136} In the corpus cavernosum the content of smooth muscle cells, endothelial cells, and elastic fibers decreases, while collagen content increases.\textsuperscript{132,135–137} Reduced production of growth factors VEGF\textsuperscript{128,138} and basic fibroblast growth factor\textsuperscript{130,139} has been implicated in the impaired function and structure of endothelial and smooth muscle cells.

The effect of hypercholesterolemia on neurogenic neurotransmission remains largely unknown. Histological studies have shown damage to dorsal and cavernous nerves, with a decrease in the number and size of unmyelinated axons.\textsuperscript{136} Future studies are needed to understand better the pathology of neurogenic ED associated with hypercholesterolemia.

Hypertension

Approximately 30% of male hypertensive patients have ED.\textsuperscript{140} Despite many epidemiologic studies showing the link between hypertension and ED, scientific studies establishing the cellular and molecular mechanisms for this link are sparse.

Both endothelium-dependent\textsuperscript{141,142} and neurogenic NO- and carbon monoxide-dependent relaxation of the corpus...
cavernosum are decreased in hypertensive rats. Vascular disturbances may result from decreased eNOS expression, increased cGMP degradation by upregulated PDE-5, and decreased NO bioavailability, and increased oxidative stress in the penis. Endothelium-independent relaxation of the erectile tissue is enhanced in spontaneously hypertensive rats, possibly as a compensatory mechanism resulting from defective endothelium-dependent relaxation. Increased peripheral vascular resistance in hypertension-associated ED is associated with increased RhoA expression and Rho-kinase activity in the penis. Angiotensin II is a potent vasoconstrictor implicated in the development and maintenance of hypertension. Within the vascular wall, angiotensin II, through the angiotensin I receptor, stimulates the production of ROS by activation of NAD(P)H oxidase. While the corpus cavernosum of spontaneously hypertensive rats exhibits increased lipid peroxidation and decreased superoxide dismutase (SOD) levels, the source of ROS has not been investigated. Blood vessels manifest decreased lumen diameter and thickening of the wall. Morphologic changes in the penis involve endothelial and smooth muscle damage, smooth muscle proliferation, increased collagen deposition, and thinning of the tunica albuginea.

### Metabolic syndrome

The metabolic syndrome (also known as syndrome X and insulin resistance syndrome) refers to a minimum of three of the following disorders, each of which is an independent risk factor for ED: abdominal obesity, hypertension, insulin resistance, high fasting blood glucose, and dyslipidemia. A high incidence of metabolic syndrome has been demonstrated in men with ED. In an animal model of metabolic syndrome, decreased erectile response has been attributed to increased smooth muscle contraction. However, the exact molecular mechanisms by which the combination of different derangements produces ED are poorly defined to date.

### Summary and conclusion

Many advances in the understanding of basic erection physiology and pathophysiology have been made in the past 10 years. These advances have revealed the complexity of regulation of erectile function, both under normal conditions and in association with various disease states. Multiple molecular pathways and mechanisms at the central nervous system level and at the peripheral level regulate the normal erectile response, and disturbances at any level will result in ED. The identification of the roles and mechanisms of action of various mediators, as well as their interactions, in normal erectile function is a major scientific development in the study of ED. However, the precise physiologic and pathophysiologic mechanisms are still incompletely known. For example, there are many unanswered questions about the role of oxidative stress and the sources of ROS in the penis, the role and regulation of the RhoA–Rho-kinase pathway, the factors involved in the regulation of eNOS and nNOS function, and the neurogenic mechanisms involved in erection biology. In addition, while many ED presentations may share similar underlying molecular derangements, recent studies have demonstrated that a unique molecular determinant or mechanism may predominate in a specific disease state. Further studies are needed to elucidate specific mechanisms associated with specific disease states. Further understanding of the molecular basis of ED may lead to the development of new therapeutic avenues based on targeting a specific mechanism associated with a specific ED condition.

### Acknowledgment

This work was supported by NIH/NIDDK grants DK067223 and DKDK064679 (to ALB), and DK075782 and DK074826 (to BM).

### REFERENCES

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ten 2006; 19: 1226–32.
Neurotransmitters in the corpus cavernosum: nitric oxide and beyond

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Introduction

Cavernous smooth muscle contraction and relaxation, and the resultant states of penile flaccidity and erection, are primarily dependent upon cytosolic calcium levels.1 Smooth muscle tone is itself regulated by the complex interplay between extracellular signals and intracellular events governing vasorelaxant and vasoconstrictive physiologic mechanisms.2 The neurotransmitters of the corpus cavernosum are responsible for smooth muscle effects via activation of downstream second messenger molecules, alteration of ion channel permeabilities, and activation of cell-to-cell communication through gap junctions.3 The primary molecular events for penile erection may be summarized as follows.

1. In the flaccid state, cavernosal smooth muscle contraction is maintained by vasoconstrictors such as norepinephrine and endothelin-1 (ET-1).4 The downstream RhoA–Rho-kinase signaling pathway maintains constriction of the cavernosal arterioles and sinusues, helping to maintain the penis in the flaccid state.5 Intrinsic myogenic activity also contributes to maintenance of smooth muscle tone.5

2. Following sexual stimulation, nitric oxide (NO) is released from non-adrenergic non-cholinergic nerve endings and the endothelium of the penis. NO is the principal neurotransmitter mediating penile erection and is synthesized by neuronal NO synthase (nNOS) and endothelial NO synthase (eNOS).6

3. NO activates the cGMP–protein kinase G (PKG) signaling cascade, resulting in corporal smooth muscle relaxation, reduced resistance of cavernosal arterioles, and increased blood flow to the corpora cavernosa.2–4 The end result is an erect penis.

4. Detumescence occurs as NO release ceases and cGMP is broken down by phosphodiesterases. In addition, sympathetic discharge occurs if sexual stimulation results in ejaculation.1

These processes are dependent upon calcium homeostasis, which is achieved in the penile smooth muscle by voltage-gated channel influx of extracellular calcium membrane-bound receptor activation allowing influx of calcium through receptor-operated channels, and specific signaling pathways stimulated by calcium release from the sarcoplasmic reticulum.5 The net response of calcium transport and calcium sensitizing mechanisms to relaxant and contractile factors determines smooth muscle tone, and thus, erectile state.4

In this chapter, the principal and secondary neurotransmitters responsible for the contraction and relaxation of cavernous smooth muscle are reviewed, as are primary mechanisms of action (cAMP and cGMP second messenger signaling systems), and the role of RhoA–Rho kinase in calcium sensitization.

Neurotransmitters of the corpus cavernosum

Flaccidity and detumescence

The primary local control of penile detumescence is adrenergic (Figure 11.1). Alpha-adrenergic nerve fibers and receptors have been identified in the cavernosal and helicine arteries, as well as in corporal smooth muscle, and norepinephrine is considered the principal neurotransmitter controlling penile flaccidity and detumescence.7 Adrenergic receptors outnumber cholinergic fibers in the penis, and receptor-binding studies have shown the ratio of alpha-adrenoceptors to beta-adrenoceptors to be almost 10:1.8 Functionally, adrenergic stimulation results in vasoconstriction of the penile arteries and contraction of the trabecular smooth muscle, causing a reduction in arterial inflow and collapse of the lacunar spaces, respectively.7,9 Trabecular smooth muscle contraction causes decompression of the drainage venules from the cavernous bodies, allowing flow to the lacunar spaces.4 Contemporary understanding of sympathetic contraction suggests that this process is mediated by activation of more than one alpha-receptor subtype sensitive to norepinephrine, as well as secondary responses to circulating catecholamines.5,10,11 Activation of postsynaptic alpha-1a and alpha-1c-adrenergic receptors (the dominant penile subtypes) provokes an initial release of intracellular calcium, followed by subsequent extracellular calcium entry for the maintenance of the contractile tone.1,12 Contraction is then modulated by presynaptic alpha-2-adrenergic receptors.13 Of note, alpha-2a, alpha-2c, and alpha-2d adrenoceptors are present on cholinergic nerve terminals within the penis, inhibiting non-adrenergic, non-cholinergic transmitter release by presynaptic norepinephrine in addition to producing postjunctional vasoconstriction;
these dual mechanisms function to maintain flaccidity. From a clinical standpoint, the physiologic importance of adrenergic signaling has been confirmed by intracavernous injection of alpha-blocking agents, such as phentolamine, and alpha-agonists, such as phenylephrine, which result in penile erection and detumescence, respectively.

Prostaglandins are derived from arachidonic acid via the cyclo-oxygenase mechanism, and several constrictor prostanoids, including prostaglandin I-2 (PGI-2), prostaglandin F-2α (PGF-2α), and thromboxane A₂ (TXA₂) are synthesized by human cavernous tissue. Production of constrictor prostanoids antagonizes effects of relaxant prostaglandins, including prostaglandin E-1 (PGE-1). In vitro studies have confirmed that prostanoids influence the tone and spontaneous activity of isolated trabecular muscle, while functional characterization of human trabecular and arterial penile smooth muscle has demonstrated that only thromboxane prostanoid receptors mediate contractile effects of prostanoids in the penis. Functionally, it has also been observed in vitro that constrictor prostanoids, when simultaneously released with NO, attenuate the dilator effect of the NO.

As angiotensin II has been identified at physiologic levels in the cavernous bodies of the human penis, the renin–angiotensin system may also play a role in the maintenance of penile smooth muscle tone. Angiotensin II, detected in both endothelial and smooth muscle cells of the corpus cavernosa, evokes in vitro contraction of human and rabbit corporal smooth muscle via angiotensin I subtype receptors. These G protein-coupled receptors mediate the contractile response through Gq stimulation and the cascade of phospholipase C activation, generation of inositol triphosphate and subsequent increase in intracellular calcium; functionally, penile injection of angiotensin II reverses spontaneous erections in dogs and, in contrast, the angiotensin I receptor antagonist losartan decreases intracavernous pressures. Physiologically, intracavernous blood levels of angiotensin II are higher than the levels in systemic peripheral blood, and the levels increase in the detumescence phase of human erection. Animal studies have also recently demonstrated that administration of an angiotensin I receptor antagonist restored erectile function in normotensive aged rats. Therefore, human and animal studies suggest that local production of angiotensin II may increase penile smooth muscle contractility by way of angiotensin I receptors, facilitating penile detumescence.

Endothelins (ET) are potent vasoconstrictor produced by the endothelial cells, occurring as three distinct subtypes: ET-1, ET-2 and ET-3. ET-1 has been suggested as a likely mediator for detumescence, because it is synthesized by the sinusoidal endothelium and possibly by trabecular muscle itself; it elicits strong in vitro contractions of corpus cavernosa smooth muscle, and it is more potent that its counterparts. Two receptors for endothelin have been identified to date. ET₁ primarily is localized in vascular smooth muscle and mediates vasoconstriction while its counterpart, ET₂, is predominantly found in the endothelium.
and mediates vasodilation of vascular tissues (local release of NO). The mechanism of intracellular transduction for both receptors is the degradation of inositol phosphate, resulting in the release of intracellular calcium and activation of protein kinase C (PKC). Endothelin has been suggested to regulate smooth muscle proliferation in the penis by regulating gene expression. It is of interest that a recently reported study demonstrated increased mean plasma levels for both ET-1 and AT-2 in patients with erectile dysfunction (ED), identifying these two molecules as exciting targets requiring further study.

Other neurotransmitters localized to the penis that demonstrate vasoconstrictor actions include neuropeptide Y, arginine vasopressin, and substance P. The clinical significance of these molecules remains to be elucidated.

In summary, current evidence suggests that maintenance of the cavernous smooth muscle in a semicontracted (flaccid penis) state is dependent upon four mechanisms:

- intrinsic myogenic activity;
- adrenergic neurotransmission;
- endothelium-derived contracting factors, such as angiotensin II, PGF-2α, and ET-1;
- and calcium-sensitizing pathways (see the section on RhoA–Rho kinase, pages 87–88).

On the other hand, and as described previously, detumescence occurs as a result of:

- the cessation of NO release;
- sympathetic discharge at ejaculation, and
- the breakdown of cGMP by phosphodiesterases.

Penile erection

Nitric oxide and the cGMP signaling pathway

Nitric oxide (NO), which is released from non-adrenergic, non-cholinergic neurotransmission and from the endothelium, is the principal neurotransmitter mediating penile erection (Figure 11.2). NO is a highly reactive and chemically unstable free radical molecule known to regulate a diverse range of physiologic functions, including smooth muscle relaxation, central and peripheral neurotransmission, platelet reactivity, and cytotoxicity of immune cells. NO increases the production of cGMP, which in turn relieves the cavernous smooth muscle; nitric oxide synthase (NOS) uses l-arginine, an amino acid, and molecular oxygen to form NO and the amino acid l-citrulline via a reaction that also requires NAD(P)H and tetrahydrobipterin substrates (Figure 11.3). Three isoforms of NOS have been identified: neuronal NOS (nNOS), endothelial NOS (eNOS), and inducible NOS (iNOS). NOS is expressed in the cholinergic nerves of the penis, while eNOS is found in the endothelium. Contemporary data suggest that nNOS-derived NO is responsible for the initiation of the smooth muscle relaxation, whereas inositol trisphosphate kinase–Akt-dependent phosphorylation and activation of eNOS leads to sustained NO production, maximal rigidity, and maintenance of erection. Both of these isoforms require calcium and calmodulin for activity. On the other hand, iNOS is calcium-independent and is upregulated following exposure to inflammatory mediators.

The cGMP signaling pathway is principally responsible for penile erection. The most physiologically relevant target for NO is soluble guanylyl cyclase (sGC); NO, because of its small size, diffuses into the cell and binds to sGC in the cytoplasm. Activation of the NO–sGC–cGMP pathway results in smooth muscle relaxation, as the ‘second messenger’ cGMP activates cGMP-dependent protein kinases, resulting in phosphorylation of specific proteins and ion channels. The soluble isoform sGC plays a pivotal role in erectile function because it provides the link between NO and cGMP, which represent the extracellular and intracellular signaling molecules for penile erection, respectively.

Protein kinase G (PKG), also known as cGMP-dependent kinase (cGK), is the principal receptor and mediator for cGMP signals. Regulation of cavernous smooth muscle tone occurs through PKG-1 alpha and beta isoforms; following activation, PKG-1 activates potassium channels and the sodium–potassium–adenosine triphosphatase (Na+–K+–ATPase) pump. Inhibition of calcium influx leads to decreased levels of intracellular calcium and cavernous smooth muscle relaxation.

In summary, activation of non-adrenergic, non-cholinergic nerves to the corpus cavernosum as a result of sexual stimulation results in NO release, activation of soluble guanylyl cyclase, and cGMP production. Subsequent downstream events lead to smooth muscle relaxation. eNOS activation in response to shear stresses to the endothelial lining contributes to rigidity and maintenance of penile erection. Phosphodiesterase-5 terminates cGMP signaling by catalyzing hydrolysis to GMP. Although the cGMP-signaling pathway is also activated by natriuretic peptides, including atrial, brain, and C-type forms, their role (if any) in physiologic penile erection remains to be determined.

The cAMP signaling pathway and penile erection

The cyclic adenosine monophosphate signaling molecules include adenosine, calcitonin gene-related peptides (CGRPs), prostaglandins, and vasoactive intestinal polypeptide (VIP). These molecules bind and activate specific cytoplasmic membrane receptors, forming ligand-receptor complexes which interact with downstream G proteins and activate adenylyl cyclase (AC) (see Figure 11.2). AC increases intracellular cAMP levels, which, in turn, activates the principal cAMP receptor, protein kinase A (PKA). PKA, also termed cAMP-dependent kinase (cAK), regulates the subsequent phosphorylation of a wide variety of cytoplasmic and nuclear compartment downstream targets. Of the more than 100 different cellular proteins identified as physiologic substrates of PKA, three substrate proteins have been identified in penile tissue: phosphodiesterases (PDEs), cAMP-responsive element-binding proteins (CREBs), and ATP-sensitive potassium (KATP) channels. Cytoplasmic levels of calcium are reduced by activated cAMP–PKA signaling, leading to cavernous smooth muscle relaxation; the role of this pathway in endogenous physiologic erection remains unclear but is probably limited to a minor role. Exogenous stimulation using agents such as PGE-1, which lead to cAMP activation, however, is a clinically robust method of eliciting an erection. cAMP is inactivated
by cleaving back to AMP by the action of cAMP-binding phosphodiesterases.  

VIP is a potent vasodilator, which is structurally related to pituitary AC-activating polypeptide (PACAP).  
The human penis is richly supplied with nerves containing VIP, including a larger percentage of corporal trabecular and perivascular nerve fibers. Interestingly, these fibers often demonstrate the presence of NOS, leading to the supposition that VIP may act with NO as a possible co-mediator of penile erection.  Unlike NO, VIP binding leads to smooth muscle relaxation through increased cAMP and PKA activation, inducing closure of calcium channels and opening of potassium channels; VIP expression also appears to be androgen-independent.  In men, intracorporeal injection of VIP has not produced rigid erection, but can improve success rates when combined with papaverine and phentolamine.  Although the role of VIP in penile erection remains incompletely elucidated, VIP release has not been shown to be essential for neurogenic relaxation of human cavernous smooth muscle to date.

The most abundant prostanoids in the smooth muscle of the human penis are PGE-1 and PGE-2. Of the four prostaglandin receptors modulating relaxation, only EP-2 and EP-4 subtypes are present in the arterial and trabecular smooth muscle of the penis.  These receptors are coupled to an alpha-containing G protein, stimulating AC to increase intracellular cAMP; PGE-1 and PGE-2 activation of the cAMP pathway
relaxes the corpus cavernosum.\textsuperscript{15} Although prostaglandins and prostaglandin receptors in erectile tissue have been clearly demonstrated, their roles in spontaneous physiologic erection are yet to be defined. On the other hand, intracorporeal injection of PGE-1 has been safely used as an effective treatment for ED worldwide for more than 20 years.\textsuperscript{49} PGE-1-induced elevation of intracellular levels of cAMP is three- to 10-fold, activating PKA and decreasing intracellular calcium levels and activating K$\text{Ca}$ channels; a secondary effect is the inhibition of norepinephrine release by binding prejunctional EP-13 receptors, which offsets corporal sympathetic tone.\textsuperscript{3,4,45}\textsuperscript{\textdagger} Transurethral application of PGE-1, although less robust than intracorporeal injection, is an effective ED treatment alternative for some men.

Calcitonin gene-related peptides (CGRP) are potent vaso-dilators released from perivascular nerve fibers and have been localized to the cavernous nerves, cavernous arteries, and corporal smooth muscle.\textsuperscript{1,3} CGRP acts through the calcitonin receptor-like receptor (CRLR), and has demonstrated a dose-related increase in penile arterial inflow and erection when administered intracorporeally in ED patients.\textsuperscript{2,4,6,67} Animal studies have shown that adenovirus-mediated gene transfer of CGRP enhances the erectile response in aged rats, apparently by increasing cAMP levels in the corpora cavernosa.\textsuperscript{46} Adenosine, acting through A2 receptors that are coupled to G$\text{i}$ proteins, has also been shown to stimulate AC and subsequent vasorelaxation. Whether adenosine plays a role in physiologic erection is unclear, since intracavernous injection in the dog has been shown to induce full erections but, in another study, treatment with the adenosine receptor inhibitor Psp-theophylline (8-SPT) did not alter pelvic nerve stimulation-induced tumescence, suggesting a lack of aden-osine involvement in this process.\textsuperscript{1,49,50} Also, intracorporeal injection of adenosine in humans has not resulted in penile erection to date.\textsuperscript{49}

Cholinergic mechanisms and nerve–neurotransmitter interactions

Acetylcholine, the primary neurotransmitter of the para-sympathetic nervous system, has been shown to be released from human erectile tissue when electrically stimulated, and before the identification of NO, it was thought to be the primary neurotransmitter responsible for physiologic erection.\textsuperscript{3,51} Although acetylcholine is not the predominant neurotransmitter, it does contribute indirectly to penile erection by acting via prejunctural muscarinic receptors to inhibit the release of norepinephrine from adrenergic neurons and stimulation of NO release from endothelial cells.\textsuperscript{1,9}

In the human corpus cavernosum, noradrenergic responses are under nitrergic control; high concentrations of norepinephrine in the penis fail to show an effect when nitrergic neurotransmission is operating.\textsuperscript{4} Adrenergic neurons, as mentioned above, can also regulate the release of NO while activation of the NO–cGMP-dependent protein kinase type 1 (cGKI) pathway leads to inhibition at several sites of the noradrenergic contractile pathway in the vascular smooth muscle by impairing phospholipase C production of inositol triphosphate, inositol triphosphate receptor activity, and the RhoA–Rho-kinase pathway.\textsuperscript{1,4,52–54} However, interaction sites have not yet been identified in penile smooth muscle, but nitrergic–noradrenergic imbalance secondary to defective nitrergic neurotransmission has been demonstrated in penile tissue from patients with ED.\textsuperscript{5,53,56} Cholinergic activity reduces constrictor (adrenergic) tone and facilitates NO-mediated smooth muscle relaxation; pharmacologic blockade of muscarinic receptors has been shown to reduced erectile response to electrostimulation of the cavernous nerves.\textsuperscript{27,57}

RhoA–Rho kinase pathway and calcium sensitization

Normal erectile function is dependent upon vasorelaxation induced by neurotransmitter release overcoming vasoconstriction of corporal smooth muscle.\textsuperscript{2} Reduced smooth muscle vasorelaxation or increased vasoconstriction leads to impaired erectile function; in contrast to the understanding of NO-induced penile smooth muscle relaxation, limited information is available on vasoconstrictive mechanisms.\textsuperscript{1,2} Several contemporary studies suggest that RhoA–Rho-kinase mediated calcium sensitization plays a significant role in the regulation of corpora smooth muscle tone and maintains the penis in the flaccid state.\textsuperscript{38–46}

Once cytosolic calcium returns to basal levels, and the penis attains the flaccid state, calcium-sensitizing pathways are the
key regulators of smooth muscle tone. The RhoA–Rho kinase pathway is able to perform this function via activation of excitatory receptors coupled to G proteins, which results in contraction by increasing calcium sensitivity but without concurrent changes in cytosolic calcium levels. Activated Rho kinase phosphorylates, and thereby inhibits, the regulatory subunit of smooth muscle myosin phosphatase. This prevents dephosphorylation of myofilaments, thus maintaining contractile tone (Figure 11.4). RhoA, a small, monomeric G protein that activates Rho-kinase, acts as the molecular switch between the inactive GDP-bound state in the cytosol and the active GTP-bound state found mainly in the plasma membrane. Rho-kinase, one of the downstream targets of RhoA, consists of alpha and beta isoforms that have been shown to be involved in erectile function. Both RhoA and Rho-kinase are expressed in penile smooth muscle; it is of interest that the amount of RhoA expressed in the cavernous smooth muscle is 17-fold higher than that in vascular smooth muscle. Once activated, RhoA–Rho-kinase enhances calcium sensitivity through phosphorylation of the myosin light chain (MLC) phosphatase targeting subunit (MYPT1), inhibiting MLC phosphatase activity. Smooth muscle contraction results as MLC phosphorylation is increased. Although increased RhoA–Rho-kinase activity has been shown to cause increased vascular tone, the function of RhoA–Rho-kinase in ED has not been fully elucidated. The emerging consensus is that tonic cavernous smooth muscle tone (the flaccid state) is governed by calcium-sensitizing pathways, most likely via RhoA–Rho-kinase signaling.


**Conclusions**

Penile erection is dependent upon cavernous smooth muscle relaxation. A large body of evidence supports NO as the key mediator of this process, as NO released by nNOS found in the cavernous nerve terminals initiates the erection and eNOS mediated NO helps maintain rigidity. The NO–cGMP signaling pathway activates protein kinase G, which acts upon potassium and calcium channels to lower cytosolic calcium levels and facilitate smooth muscle relaxation. Phosphodiesterases hydrolyze cGMP to GMP, allowing for cavernous smooth muscle to regain tone (flaccid state) as cytosolic calcium levels increase; PDE-5 inhibitors used for the treatment of ED inhibit the catalytic activity of phosphodiesterase on cGMP. Cytoplasmic levels of calcium are also reduced by activated cAMP–PKA signaling, leading to cavernous smooth muscle relaxation. The role of this pathway, which may be activated by CGRP, prostanooids, VIP, and adenosine, remains unclear for physiologic erections, but is probably limited to a minor role. From a practical standpoint, the use of intracavernosal (exogenous) PGE-1 to activate cAMP signaling has proven to be a safe and robust treatment for ED of various underlying etiologies.

Maintenance of the semicontracted, flaccid state is dependent upon several mechanisms that regulate cavernous smooth muscle tone. These include intrinsic myogenic activity, adrenergic neurotransmission, endothelium-derived contracting factors such as angiotensin II, PGF-2α, and ET-1, and calcium-sensitizing pathways. Emerging evidence suggests that the RhoA–Rho-kinase signaling pathway may be the primary determinant of tonic contraction.

Impairment of neurogenic and endothelium-dependent NO release or dysregulation of cavernosal neurotransmitter function may result in an imbalance between smooth muscle vasorelaxation and increased vasoconstriction, leading to impaired erectile function. Advances in the understanding of penile neurobiology and its relationship to erectile function (and dysfunction) have identified several candidate neurotransmitters as potential targets for ED treatments; in most cases, however, their roles in the erectile process and as candidate therapies remain to be determined.

**REFERENCES**


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Neurotransmitters in the corpus cavernosum: nitric oxide and beyond


and


12 Receptor pharmacology related to erectile dysfunction

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Introduction

Penile erection is initiated after central processing and integration of stimuli (e.g. tactile, visual, olfactory, and imaginative). Signals are generated to the peripheral tissues and the final response is mediated by co-ordinated spinal activity in the autonomic pathways (to the penis) and somatic pathways (to the perineal striated muscles). The central regulation of penile erection involves many transmitters and transmitter systems, the details of which are still not completely known. Some of the anatomical areas of the brain that relate to sexual function have been defined, including the medial amygdala, medial preoptic area (MPOA), paraventricular nucleus (PVN), periaqueductal gray, and ventral tegmentum.\(^1\)\(^-\)\(^3\) In rats, electrical stimulation of the MPOA,\(^4\) the PVN,\(^5\) or the hippocampal formation\(^6\) can elicit an erectile response.

Spinally, there seems to be a network consisting of primary afferents from the genitals, the spinal interneurons, and the sympathetic, parasympathetic, and somatic nuclei. This network appears capable of integrating information from the periphery and eliciting reflexive erections; and it also seems to be the recipient of supraspinal information.\(^7\) The degree of preservation of sensory function in the T11–L2 dermatomes could be used to determine the potential for psychogenic erectile responses in men with spinal cord injury.\(^8\)

Peripherally, the balance between factors that control the degree of contraction of the smooth muscle of the corpora cavernosa determines the functional state of the penis. Many details of neurotransmission, impulse propagation, and intracellular transduction of signals in penile smooth muscles remain to be elucidated. However, the information on both central and peripheral control mechanisms involved in erection is rapidly expanding, and new details are continuously added.\(^9\)\(^-\)\(^16\)

Central neuromediation

The central mechanisms controlling erection include supraspinal as well as spinal pathways. The current knowledge about these mechanisms is largely based on experimental data from animals (mainly rats).

Oxytocin

Oxytocinergic spinal projections from the supraoptic and paraventricular nuclei of the hypothalamus are likely to influence the sacral autonomic outflow more than the somatic outflow.\(^17\)\(^,\)\(^18\) The finding that immunoreactive oxytocin-containing spinal neurons associate with sacral preganglionic neurons supports the idea that oxytocin has an important role in the autonomic spinal circuitry that mediates penile erection.\(^19\)\(^,\)\(^20\)

Oxytocin is a potent inducer of penile erection when injected into the lateral cerebral ventricle, the PVN, or the hippocampus of laboratory animals; intrathecal oxytocin can also initiate an erection. These erections can be blocked by the administration of oxytocin antagonists given intracerebroventricularly or intracereally, or by electrolytic lesion of the PVN. Additionally, non-contact erections can be reduced by a selective oxytocin receptor antagonist administered into the lateral ventricles, which supports the view that oxytocin mediates this response.\(^21\)

Succu et al. (2007) analyzed the effect of proerectile doses of the selective dopamine D4-agonist PD-168077 and apomorphine, a mixed dopamine receptor agonist, injected into the PVN, on the concentration of extracellular dopamine and its main metabolite, 3,4-dihydroxy-phenylacetic acid (DOPAC), in the nucleus accumbens in male rats.\(^22\) Both drugs induced penile erection episodes that were reduced to various extents by D2–D3 and D4 antagonists. The proerectile effect and the concomitant increase in dopamine and DOPAC concentration in the nucleus accumbens dialysate were almost completely abolished by the potent oxytocin receptor antagonist d(CH\(^2\))\(^2\)Tyr(Me)\(^2\)Orn\(^4\)-vasotocin, given into the lateral ventricles. The authors concluded that stimulation of dopamine receptors (mainly of the D2 to D4 subtype) in the PVN induces the release of oxytocin in brain areas that influence the activity of the mesolimbic dopaminergic neurons that mediate the appetitive and reinforcing effects of sexual activity.

Oxytocin increases nitric oxide (NO) production in the PVN.\(^13\)\(^,\)\(^23\) and nitric oxide synthase (NOS) inhibitors prevent penile erection and yawning in rats induced by oxytocin, dopamine, excitatory amino acids, m-chlorophenylpiperazine [m-CCP, a 5-hydroxy triptamine (5-HT)\(^2\)C receptor agonist], and adrenocorticotropic hormone (ACTH)—alpha-melanocyte stimulating hormone (MSH). Yawning is a phylogenetically old,
stereotyped event that occurs alone or associated with stretching or penile erection in humans and animals under various conditions.\textsuperscript{24} It has been suggested that NO acts as an intracellular rather than an intercellular modulator inside the paraventricular oxytocinergic neurons in which NO is formed to facilitate the expression of this phylogenetically old event by guanylate cyclase-independent mechanisms.\textsuperscript{24,25} It is likely that this involves the parvocellular neuron population within the nucleus.\textsuperscript{25}

Plasma oxytocin concentrations are known to be elevated following sexual stimulation in humans;\textsuperscript{1} however, the relevance of the oxytocinergic pathway has never been established. This makes it of interest to explore the therapeutic potential of this system.

**Dopamine**

Central dopaminergic neurons project to the MPOA and the PVN.\textsuperscript{26} Furthermore, dopaminergic neurons have been identified that travel from the caudal hypothalamus to innervate the autonomic and somatic nuclei in the lumbosacral spinal cord.\textsuperscript{27-29} Thus, dopamine can be expected to participate in the regulation of both the autonomic and somatic components of the penile reflexes.

Both the two major families of dopamine receptors, the D1-like receptors (D1, D5) and the D2-like receptors (D2, D3, and D4)\textsuperscript{30} have been associated with central erectile functions; however, the D2-like receptor subtype seems to have the predominating effect. The non-selective dopamine receptor agonist, apomorphine, when administered systemically to male rats, was found to induce penile erection,\textsuperscript{30} simultaneously producing yawning and seminal emission. Similarly, low-dose systemic administration of other dopamine agonists initiates erection.\textsuperscript{1} The effects of these agonists can be attenuated by centrally acting, but not by peripherally acting, dopamine receptor antagonists.

Injection of apomorphine into the MPOA demonstrated that low levels of dopaminergic stimulation, via D1 receptors in particular, facilitated erections.\textsuperscript{31} In contrast, dopaminergic antagonists injected into the MPOA decreased the number of penile reflexes.\textsuperscript{32,33} In the PVN, similar experiments have established that D2-like receptors, rather than D1-like receptors, primarily facilitate erections.\textsuperscript{1}

The erection following paraventricular D2-like receptor stimulation apparently involves oxytocinergic neurotransmission. Dopaminergic neurons impinge on oxytocinergic cell bodies in the PVN,\textsuperscript{34,35} and apomorphine-induced penile erection is prevented dose-dependently by oxytocin receptor antagonists\textsuperscript{36} or by electrolytic lesions of the PVN that deplete the oxytocin content.\textsuperscript{1,37-39} Conversely, injection of oxytocin into the PVN induced erections that were not attenuated by dopamine receptor blockade, suggesting that dopaminergic neurons activate oxytocinergic neurons in the PVN, and that released oxytocin then accounts for the erectile response. Melis et al. showed that penile erections in male rats induced by selective dopamine D4 agonists were reduced by selective dopamine D4 antagonists, voltage-dependent calcium channel blockers, neuronal NOS (nNOS) inhibitors, and oxytocin receptor antagonists given in the lateral ventricles, but not in the PVN.\textsuperscript{40} Martino et al. investigated central oxytocinergic and dopaminergic mechanisms regulating penile erection in conscious rats and concluded that proerectile activity mediated via D2-like receptors (and possibly via D4-like receptors) may be dependent on supraspinal and spinal oxytocin receptors, and that oxytocin-mediated erection (supraspinal and spinal) requires basal D2-like receptor (and possibly D4-like receptor) activation.\textsuperscript{41} The same group aimed to identify D4 receptor signal transduction pathways in vivo.\textsuperscript{42} They showed that the selective dopamine D4 agonist PD168077 induced c-Fos expression and extracellular signal regulated kinase (ERK) phosphorylation in the PVN. The selective dopamine D4 receptor antagonist A-381393 blocked both c-Fos expression and ERK-1 and ERK-2 phosphorylation produced by PD168077. In addition, PD168077-induced ERK-1 and ERK-2 phosphorylation was prevented by SL327, an inhibitor of ERK-1 and ERK-2 phosphorylation. Interestingly, treatment with A-381393 alone significantly reduced the amount of Fos immunoreactivity compared with basal expression observed in vehicle-treated controls. Dopamine D4 receptor and c-Fos co-expression in the PVN was observed using double immunohistochemical labeling, suggesting that PD168077-induced signaling may result from direct dopamine D4 receptor activation. The authors concluded that these results demonstrate functional dopamine D4 receptor expression and natural coupling in the PVN that is linked to signal transduction pathways that include immediate early gene and MAP kinase activation. Furthermore, the ability of the selective dopamine D4 antagonist A-381393 alone to reduce c-Fos expression below control levels was interpreted to indicate the presence of a tonic dopamine D4 receptor activation under basal conditions in vivo.

Brioni et al. reported that the dopamine D4 receptor plays a role in the regulation of penile function using a selective dopamine D4 receptor agonist, ABT-724, with no effect on dopamine D1, D2, D3, or D5 receptors.\textsuperscript{43} ABT-724 facilitated penile erection in a dose-dependent fashion when given subcutaneously to conscious rats, an effect that was blocked by haloperidol and clozapine (acting centrally and peripherally) but not by domperidone (acting only peripherally). A proerectile effect was observed after intracerebroventricular, but not intrathecal, administration, suggesting a supraspinal site of action. The drug seemed to be without emotive effects in a ferret model of emesis,\textsuperscript{44} and it was suggested that ABT-724 could be useful for the treatment of erectile dysfunction (ED).

The same group identified a structurally distinct D4-selective agonist with superior oral bioavailability to that of ABT-724 for the potential treatment of ED. Optimization with the (N-oxy-2-pyridinyl) piperidine template led to the discovery of ABT-670, which exhibited excellent oral bioavailability in the rat, dog, and monkey (68%, 85%, and 91%, respectively) with comparable efficacy, safety, and tolerability to that of ABT-724.\textsuperscript{45} Injection of apomorphine into the lumbosacral subarachnoid space was reported to impair ex copula (i.e. outside the context of copulation) penile reflexes, slow the rate of copulation, and decrease the number of intromissions preceding ejaculation,\textsuperscript{46,47} suggesting an inhibitory effect on spinal erectile mechanisms. This is in contrast to recent findings showing that intrathecal injection of apomorphine in rats evokes erection in both normal animals and in animals in which the spinal cord has been transected.\textsuperscript{46,48} Most likely,
stabilize the dopaminergic system can produce erection both at supraspinal and spinal sites.

As mentioned above, systemically administered apomorphine enhances seminal emission. Pehek et al. found that apomorphine injected into the PVN, but not into the MPOA, enhanced seminal emission.\(^4\) Recording of intracavernosal pressure in the non-anesthetized rat after systemic administration of apomorphine showed that the pressure response consisted of both smooth and striated muscle components.\(^5\) This implies that systemic apomorphine has effects not only on the sacral parasympathetic output, but also on somatic pathways.

**Adrenocorticotropic and related peptides**

Intracerebroventricular administration of ACTH and alpha-MSH induces penile erection – along with grooming, stretching, and yawning.\(^6\) These effects are most probably mediated via stimulation of melanocortin (MC) receptors, of which five different subtypes have been cloned and characterized.\(^7\) Alpha-MSH–ACTH seem to act in the hypothalamic periventricular region, and grooming, stretching, and yawning, but not penile erection, was reported to be mediated by MC\(_3\) receptors.\(^8\) It is unclear, however, what MC receptor subtype or subtypes can be linked to the erectile responses. For example, the MC\(_1\) receptor is found in high density in the hypothalamus and limbic systems,\(^9\) regions known to be important for erectile functions. The site and mechanism of action of alpha-MSH–ACTH seem to be different from those involving dopamine or oxytocin.\(^10\)

Martin et al. concluded that current evidence indicates that the MC\(_2\) receptor subtype contributes to the proerectile effects observed with melanocortin pan-receptor agonists.\(^11\) However, the putative receptor subtypes, pathways and mechanisms implicated in mediating the proerectile effects of melanocortin remain to be fully elucidated.

Melanotan II, a synthetic analog of alpha-MSH, when given subcutaneously, was shown to have proerectile effects in men with psychogenic impotence.\(^12\) Still the therapeutic potential of alpha-MSH analogs remains to be established.\(^13\)

**Excitatory amino acids**

Microinjections of l-glutamate into the MPOA elicits an increase in intracavernous pressure,\(^4\) and behavioral studies have shown that N-methyl-D-aspartate (NMDA) increases the number of penile erections when injected into the PVN.\(^14\) Furthermore, NMDA, amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid (AMPA), or trans-1-amino-1,3-cyclopentadecarboxylic acid (ACPD) increases intracavernosal pressure when injected into the PVN.\(^15\) The effect of NMDA was prevented by intracerebroventricular administration of an oxytocin antagonist.\(^16\) The NOS signal transduction pathway is considered to mediate the effect of NMDA. Injection of the amino acid leads to an increased concentration of NO metabolites in the PVN,\(^17\) and the administration of NOS inhibitors, both into the PVN and intracerebroventricularly, blocked the NMDA effect.\(^18\)

**Nitric oxide**

Several investigators have shown that within the central nervous system (CNS), NO can modulate sexual behavior and penile erection.\(^19\)–\(^23\) NO may act in several discrete brain regions, such as the MPOA\(^24\) and the PVN.\(^25\) NO production increases in the PVN of male rats during non-contact penile erections and copulation, confirming that NO is a physiological mediator of penile erection at the level of the PVN.\(^26\)

As mentioned previously, injection of NOS inhibitors intracerebroventricularly or in the PVN prevents penile erectile responses induced by dopamine agonists, oxytocin, and NMDA in rats. NO may also mediate the actions of ACTH–alpha-MSH and 5-HT–2C agonists, which elicit erections when injected into the intracerebroventricular system, according to mechanisms unrelated to oxytocinergic neurotransmission.\(^27\) The inhibitory effect of NOS inhibitors was not observed when these compounds were injected concomitantly with \(\lambda\)-arginine, the substrate for NO.\(^28\)

Zheng et al. examined the role of NO within the central nervous system component of the behavioral responses, including erection in diabetic rats.\(^29\) Four weeks after streptozotocin (STZ) and vehicle injections, NMDA-induced erection, yawning, and stretch responses through the PVN were significantly blunted in diabetic rats compared with control rats. Examination of nNOS protein by Western blot analysis indicated a reduced amount of nNOS protein in the PVN of rats with diabetes compared with control rats. Furthermore, restoring nNOS within the PVN by gene transfer using adenoviral transfection significantly restored the erectile and yawning responses to NMDA in diabetic rats. The authors concluded that a blunted NO mechanism within the PVN may contribute to NMDA-induced ED observed in diabetes mellitus.

**Serotonin**

Neurons containing serotonin (5-HT) can be found in the medullary raphe nuclei and ventral medulla reticular formation (including the rostral nucleus paragigantocellularis), and bulborespiratory neurons containing 5-HT project to the lumbar spinal cord in the rat and cat.\(^30\) Some serotonergic fibers occur in close apposition to sacral preganglionic neurons and motor neurons, and synapses were demonstrated at the ultrastructural level.\(^31\) These morphological findings support the involvement of 5-HT in both the supraspinal and spinal pharmacology of erection, with participation in both the sympathetic and parasympathetic outflow mechanisms.

In animals, 5-HT seems to exert a general inhibitory effect on male sexual behavior,\(^32\) although the amine may be inhibitory or facilitatory depending upon its action at different sites and at different 5-HT receptors within the CNS.\(^33\) This may explain conflicting reports of 5-HT agonists either enhancing or depressing sexual function. Yonezawa et al. found that p-chloroamphetamine (PCA), an indirect 5-HT agonist, elicited both penile erection and ejaculation simultaneously in anesthetized rats.\(^34\) It was suggested that these effects were mainly produced by the release of 5-HT as limited to the lower spinal cord or peripheral sites (or both). The use of selective 5-HT receptor agonists and antagonists can reveal different components of male copulatory behavior.\(^35\)
Kimura et al. investigated the effects of the novel 5-HT\textsubscript{2C} receptor agonist YM348 on intracavernosal pressure in anesthetized rats.\textsuperscript{76} YM348 induced penile erection and increases in intracavernosal pressure, and it was significantly inhibited by the selective 5-HT-2C receptor antagonist SB242084. YM348 decreased the latency of intracavernosal pressure but did not affect the quality of its duration, peak pressure, and area under the curve, even at the highest dose. The authors concluded that activation of the 5-HT-2C receptor increased intracavernosal pressure and, as a result, induced penile erection.

5-HT-2C receptors seem to mediate erectile responses,\textsuperscript{77} and stimulation of 5-HT-2C receptors increased circulating oxytocin.\textsuperscript{78} NOS inhibitors administered intracerebroventricularly prevented 5-HT-2C-receptor-mediated erectile responses.\textsuperscript{67} These findings suggest that both oxytocin and NO are involved in 5-HT-2C-receptor-mediated erections.

**Norepinephrine**

The information on noradrenergic mechanisms involved in the central neuromodulation of penile erection is sparse; however, the current data suggest that increased noradrenergic activity stimulates, whereas decreased noradrenergic activity inhibits sexual function.\textsuperscript{7,22,79}

**Gamma-aminobutyric acid**

Cumulative data resulting from investigations on the role of gamma-aminobutyric acid (GABA) in penile erection indicate that this neurotransmitter may function as an inhibitory modulator in the autonomic and somatic reflex pathways involved in penile erection.\textsuperscript{80} Activation of GABA(A) receptors in the PVN reduced apomorphine-, NMDA-, and oxytocin-induced penile erection and yawning in male rats.\textsuperscript{80} Dorfman et al. (2006) examined age-related changes of the GABA(B) receptor in the lumbar spinal cord of Sprague-Dawley rats of different ages using quantitative autoradiography.\textsuperscript{81} GABA(B) receptor affinity showed significant age-dependent and regional increases. However, the decrease in GABA(B) receptors in aged rats did not seem to be related to the inhibitory function in penile erection.

**Cannabinoids**

Administration of endogenous and exogenous cannabinoids was shown to be associated with changes in penile erection and modulation of male sexual behavior.\textsuperscript{82,83} The cannabinoid CB-1 receptor antagonist SR141716A was shown to potentiate the penile erection responses to apomorphine in rats.\textsuperscript{84} It was also shown that cannabinoid CB-1 receptors present in the PVN may influence erectile function and sexual activity, possibly by modulating paraventricular oxytocinergic neurons that mediate erectile function.\textsuperscript{85} It was demonstrated that SR141716 induced penile erection by a mechanism that involves excitatory amino acid neurotransmission causing activation of nNOS in paraventricular oxytocinergic neurons.\textsuperscript{86}

**Opioid peptides**

Available information supports the hypothesis that opioid \(\mu\)-receptor stimulation centrally prevents penile erection by inhibiting mechanisms that converge upon central oxytocinergic neurotransmission.\textsuperscript{1} In rats, morphine injected into the PVN prevents non-contact penile erections (i.e. when penile erection is induced in the male by the presence of an inaccessible receptive female) and impairs copulation. These morphine effects are apparently mediated by prevention of the increased NO production that occurs in the PVN during sexual activity.\textsuperscript{87} Morphine also prevents apomorphine-, oxytocin-, NMDA-, and non-contact-induced penile erection and yawning by inhibiting NOS activity in the PVN.\textsuperscript{88–90}

**Prolactin**

Long-term hyperprolactinaemia can depress sexual behavior, reduce sexual potency in men, and depress genital reflexes in rats.\textsuperscript{7,91} Acute and chronic central prolactin treatment in rats, however, may have, respectively, stimulatory and inhibitory effects on male sexual behavior.\textsuperscript{92} Correspondingly, striatal dopaminergic activity was shown to be increased and decreased by acute and 5-day central prolactin treatment,\textsuperscript{92} supporting the view that the effects of prolactin are associated with changes in striatal dopaminergic activity. Prolactin has been shown to inhibit the dopaminergic incertohypothalamic pathway to the MPOA.\textsuperscript{93}

In humans, it is still unclear whether the negative effects of hyperprolactinemia on erectile function are mediated centrally by way of reduction in sexual interest and sex drive,\textsuperscript{94} or through a direct effect of prolactin on corpus cavernosum smooth muscle contractility. In dogs, a direct effect on the corpus cavernosum was suggested.\textsuperscript{95} In any case, the effect seems independent of circulating testosterone levels and gonadal axis function.\textsuperscript{96}

Paick et al. evaluated 261 men for anthropometry, hormone levels, metabolic profiles, and lifestyle factors.\textsuperscript{97} Erectile function was evaluated using the self-administered International Index of Erectile Function. Patients were classified into two groups based on the six-item erectile-function domain, as those with sexual activity and those without. The authors found a significant difference in mean prolactin level between patients with sexual activity and those without. A higher prolactin level was associated with a greater likelihood of sexual inactivity. Thus, prolactin levels might play a role in sexual activity in men with ED.

**Sex hormones**

Androgens, particularly testosterone, are necessary (though not sufficient) for sexual desire in men. They are essential in the maintenance of libido and have an important role in regulating erectile capacity.\textsuperscript{98–102} In men with normal gonadal function, however, there is no correlation between circulating testosterone levels and measures of sexual interest, activity, or erectile function.\textsuperscript{103} Following castration in the male (which may reduce plasma testosterone levels by 90%),\textsuperscript{104} or other causes leading to a reduction in androgen levels, there is generally a decline in libido, and sometimes in erectile and
ejaculatory functions. Testosterone administration restores sexual interest and associated sexual activity in hypogonadal or castrated adult men.105-107 The testosterone dose–response relationships for sexual function and visuospatial cognition differ in older and young men, with higher testosterone doses being needed in the elderly for normal sexual functioning.101 El-Sakka et al. assessed the pattern of age-related testosterone depletion in patients with ED.106 They found a significant decrease in testosterone level throughout the 4-year follow up in patients with ED. Patients with decreasing testosterone were older than patients with a steady testosterone level.

When castration has been performed in humans, the resultant sexual function may range from a complete loss of libido to continued normal sexual activity. Thus, the role of androgens in erectile function is complex, and androgen deprivation may not always cause erectile dysfunction, either in humans109 or in rats.110 Suzuki et al. studied the effects of castration and testosterone replacement on intracavernosal pressure elicited with electrical stimulation of the MPOA and cavernous nerve in castrated male rats with and without testosterone replacement.111 The erectile response was expressed as the ratio of the intracavernous pressure to the blood pressure. The ratios during cavernous nerve stimulation of the animals at 2, 4, and 8 weeks after castration were significantly lower than those of the intact animals. However, the erectile responses were not eliminated. In contrast to these peripherally evoked responses, erectile responses elicited by electrical stimulation of the MPOA were eliminated following castration. After testosterone replacement, both erectile responses were restored. The authors therefore concluded that testosterone plays important roles in both the central and peripheral neural pathways for the maintenance and restoration of erectile capacity.

In hypogonadal men, it is known that exogenous testosterone administration stimulates both sleep-related erections and erectile responses to visual erotic stimulation.112-114 Serum testosterone levels, however, have to fall to well below the lower end of the normal laboratory range before nocturnal penile tumescence is impaired.115 In healthy men, testosterone enhances sexual desire and the rigidity of nocturnal penile tumescence, and leads to more rigid spontaneous erections with longer duration.114,116 It is therefore possible that testosterone acts on the motor neurons that supply the striated muscles of the penis. Other reports suggested that the site of androgen action within the penile tissue might be on the pre-erectic postganglionic parasympathetic neurons.117 Castration studies in rats revealed that testosterone deprivation might alter the dorsal nerve ultrastructure, since the diameter of both myelinated and unmyelinated axons appeared smaller as assessed by transmission electron microscopy.118 Spontaneous nocturnal erections are androgen-dependent102,103 they are impaired in states of androgen deficiency and restored with androgen replacement. Erections in response to visual erotic stimuli, on the other hand, are partly independent of androgens119,120 They persist in hypogonadal men and are not altered by androgen replacement.112,112 Thus, there may be one androgen-dependent system in the brain subserving sexual arousal and sexual desire, and one androgen-independent involving response to moving visual stimuli.119 Yassin et al. treated hypogonadal men with ED with intramuscular long-acting testosterone undecanoate.122 In all patients, serum testosterone levels were restored to normal within 6–8 weeks. Restoring testosterone levels to normal in men with proven subnormal testosterone levels was found to improve libido in most subjects and to improve erectile function in more than 50% of these men. It may take 12–24 weeks before the effects of testosterone manifest themselves. Furthermore, in normal subjects, it has been shown that there is a relationship between bioavailable testosterone and the frequency, duration, and degree of nocturnal penile tumescence.116,123 Other studies performed in eugonadal men have shown that high testosterone may promote sexual arousal with no significant changes in sexual activity.124 Several studies, however, suggest that testosterone replacement therapy in relatively modest deficiency states may improve erections in a minority of patients.120,121,125,126

Data from the Massachusetts Male Aging Study revealed the association between ED and total testosterone, bioavailable testosterone, sex hormone-binding globulin, and luteinizing hormone (LH).127 The authors concluded that there was no association among total testosterone, bioavailable testosterone, sex hormone-binding globulin, and ED. However in men with an increased level of LH, testosterone levels were associated with a decreased risk of ED.

Sex hormones can induce structural changes in the nervous system, including alterations in cell size and number, neural connectivity, and neural sprouting.128-131 These changes, which may result in sex differences (sexual dimorphism), are obvious in most mammalian species during the prenatal or early postnatal periods. There is evidence, however, that brain regions containing sex hormone-accumulating neurons in adult animals possess a considerable plasticity in response to sex steroids, and that androgens have the potential to stimulate the growth of neuronal processes and remodel neural circuits also in the adult brain.132-134 Naturally occurring, socially induced changes in androgen levels were not shown to induce morphological changes of the motor neurons of the spinal nucleus of the bulbocavernosus muscle.135

The MPOA of rats and the spinal nucleus of the bulbocavernosus1 are sexually dimorphic model systems that have been well investigated. In humans, the localization and morphology of neurons innervating the small, striated pelvic muscles correspond to that of Onuf’s nucleus X.136,137 This nucleus, similar to its rat homolog (the spinal nucleus of the bulbocavernosus), contains fewer motor neurons in the female than in the male.138

Peripheral neuromediation

The different structures of the penis receive sympathetic, parasympathetic, somatic, and sensory innervation.1,139 The nerves contain different transmitters, and the nerve populations have been categorized as adrenergic or cholinergic or non-adrenergic, non-cholinergic (NANC). It should be stressed that these nerves often contain more than one transmitter or transmitter–modulator generating enzymes, such as NOS and heme oxygenases (HO). One important population of nerves in the corpora cavernosa contains not only acetylcholine, but also NOS, vasoactive intestinal polypeptide (VIP), and neuropeptide Y.140,141 If co-released, the different transmitters–modulators
may interact, implying that the end result may be more complex than would be suggested from an experimental situation, where often the effect of a single agent is investigated.

It is not only the nerves, but also the endothelium of the vasculature of the penis that produces and releases transmitters and modulators that can influence the contractile state of the corpus cavernosum smooth muscle. In addition they may also have other important functions.

**Norepinephrine and alpha-adrenoceptors**

It is generally accepted that the penis is kept in the flaccid state mainly via a tonic activity in adrenergic nerves releasing norepinephrine.142 Norepinephrine stimulates alpha-adrenoceptors (ARs) in the penile vasculature and in the corpus cavernosum, producing contraction. Both alpha-1-ARs and alpha-2-ARs have been demonstrated in human corpus cavernosum tissue, but available information supports the view of a functional predominance of alpha-1-ARs. This may be the case also in the penile vasculature, although a contribution of alpha-2-ARs to the contraction induced by norepinephrine and electrical stimulation of nerves cannot be excluded.141

The mRNAs of all the subtypes of alpha-1-AR with a high affinity for prazosin (alpha-1A-, alpha-1B-, and alpha-1D-ARs) have been demonstrated in human corporal tissue. However, Goepel et al. have shown that alpha-1A, alpha-1B, and alpha-2A receptor protein were predominantly expressed, and that the alpha-1D-AR is present only at the mRNA level.141 The functional alpha-1-AR proteins in human corpus cavernosum tissue were characterized by Traish et al. using receptor-binding and isometric tension experiments.141 Their results demonstrated the presence of alpha-1A-, alpha-1B-, and alpha-1D-ARs, and they suggested that the norepinephrine-induced contraction in this tissue is mediated by two or possibly three receptor subtypes.

An additional alpha-1-AR subtype with low affinity for prazosin (alpha-1L), probably representing a conformational state of the alpha-1A-AR, has been suggested to be of importance in human penile erectile tissues.141 In rats, alpha-1B- and alpha-1L-AR subtypes seem functionally relevant for erectile function, and alpha-1B- or alpha-1L-AR subtype selective antagonists (or both) were suggested to represent advantages in the treatment of ED.146 The distribution of alpha-1-AR subtypes in the penis and systemic vasculature, however, may not be the same in rats and humans, and the method of study may influence the results. For example, Hussain and Marshall found that the alpha-1D-AR predominated in several systemic rat vessels in vitro,147 which may not be the case in humans.148 Similarly, Tong and Cheng found alpha-1A-ARs to be responsible for the contractile response of rat corpus cavernosum,149 which does not seem to be in agreement with the in vivo data.

Expression of mRNA for alpha-2A-, alpha-2B-, and alpha-2C-ARs in whole human corpus cavernosum tissue has been demonstrated. Radioligand binding revealed specific alpha-2-AR binding sites, and functional experiments showed that the selective alpha-2-AR agonist, UK 14,304, induced concentration-dependent contractions of isolated strips of human corpus cavernosum smooth muscle.150 Whether or not these alpha-2-ARs are of importance for the contractile regulation of tone in corpus cavernosum smooth muscle is still unclear. Prejunctional alpha-2-ARs have been shown to inhibit stimulus-evoked release of norepinephrine from nerves in the human corpus cavernosum. Stimulation of prejunctional alpha-2-ARs in horse penile resistance arteries was also shown to inhibit NANC-transmitter release.151 This might be one of the mechanisms by which norepinephrine maintains detumescence. Morton et al. assessed the response of dorsal and cavernous penile arteries on alpha-AR-selective agonists and antagonists in the rabbit.152 They found a predominant, functional alpha-1A-AR population with little evidence of other alpha-1A-AR subtypes in cavernous arteries; there seems to be evidence for the presence of alpha-2-AR in dorsal arteries. The authors concluded that alpha-agonists with affinity for alpha-1A- or alpha-2-ARs would potentially have proerectile properties.

**Endothelins and endothelin receptors**

Endothelins (ETs) have been demonstrated in penile erectile tissues and may contribute to the maintenance of corporal smooth muscle tone.1 Cultured endothelial cells from the human corpus cavernosum, but not non-endothelial cells, express ET-1 mRNA. In the endothelium of human cavernous tissue, intense ET-like immunoreactivity has been observed; immunoreactivity has also been observed in the cavernous smooth muscle. Binding sites for ET-1 have been demonstrated by autoradiography in the vasculature and cavernous tissue. As both ET-A and ET-B receptors have been found in human corporal smooth muscle membranes, it cannot be excluded that both receptor subtypes are functional.

ET-1 potently induces slowly developing, long-lasting contractions in different smooth muscles of the penis: muscles in the corpus cavernosum, cavernous artery, deep dorsal vein, and penile circumflex veins.1 Contractions can also be evoked in human corpus cavernosum tissue by ET-2 and ET-3, although these peptides have a lower potency than ET-1.153 The contractions induced by ET-1 are dependent on both transmembrane calcium flux (through voltage-dependent or receptor-operated calcium channels, or both) and on the mobilization of inositol trisphosphate-sensitive intracellular calcium stores.1

Mumtaz et al. assessed the effect of ET-1 and its possible role in the alpha-1-AR pathway during the erectile process by using organ bath studies of cavernosal smooth muscle contraction in the rat.154 ET-B receptors were found to play a greater role than ET-A receptors in ET-1-induced rabbit cavernosal smooth-muscle contraction and the detumescence process. The alpha-1-AR-dependent pathway did not involve the ET-A or ET-B receptors.

Even if much available in vitro information suggests that ETs may be of importance for erectile physiology and pathophysiology, the role of the peptides in vivo is unclear. Blockade of the ET-A receptor or the ET-B receptor has no effect on the erectile response induced by maximal ganglionic stimulation in rats.155 This may seem to reflect a minimal role of ET-1 in the erectile response in the rat; however, the results do not rule out that ETs may play a role in keeping the penis in a flaccid state, or that ETs may be associated with ED.
In a rat model of chronic cocaine administration, Kendirci et al. found significantly increased plasma big-ET-1 levels in the cocaine treatment group compared with control animals. In the penis, cocaine administration significantly increased ET₁ receptor expression compared with saline controls, while ET₄ receptor expression was not altered. Cocaine-treated rats showed also significantly decreased endothelial NOS (eNOS) expression and NO production. The authors concluded that cocaine administration significantly reduces erectile function in rats. The pathophysiologic mechanisms that are probably involved include increased plasma big-ET-1 levels, increased penile ET₁ receptor expression, and reduced penile eNOS expression.

ETs may function not only as a long-term regulator of corporal smooth muscle tone, but also as a modulator of the contractile effect of other agents, such as norepinephrine, or as a modulator of cellular proliferation and phenotypic expression.

Acetylcholine and cholinergic receptors

The importance of parasympathetic nerves for producing penile erection is well established. Penile tissues from humans and several animal species are rich in cholinergic nerves, from which acetylcholine can be released by transmural electrical field stimulation. In isolated corpus cavernosum cells, carbachol consistently produces contraction. This means that relaxation induced by acetylcholine can be obtained by inhibition of the release of a contractant factor, such as norepinephrine, or else it is produced by the release of a relaxation-producing factor, such as NO.

Bozkurt et al. analyzed the presence of neuronal nicotinic acetylcholine receptors in rabbit corpus cavernosum tissue and the possible mechanisms underlying the potentiation of electrical field stimulation-induced relaxation by nicotine. The authors showed that nicotine acts on the nicotinic acetylcholine receptors located on the nitrergic nerves, thereby evoking the release of NO from these nerve terminals and so inducing relaxation response in rabbit corpus cavernosum tissue. It is important to stress that parasympathetic nerve activity is not equivalent to the actions of acetylcholine; other transmitters may be released from cholinergic nerves. Para sympathetic activity may produce penile tumescence and erection by inhibiting the release of norepinephrine through stimulation of muscarinic receptors on adrenergic nerve terminals or by releasing NO and vasodilating peptides from nerves and endothelium (or both).

Nitric oxide and the guanylate cyclase–cGMP pathway

It is widely accepted that NO plays an important role in the relaxation of the corpus cavernosum smooth muscle and vasculature. In vitro, several investigators have shown that both acetylcholine-mediated and neurally mediated relaxation in animal and human corpus cavernosum involves the release of NO, or a NO-like substance. Both the nerves (nNOS) and the endothelium (eNOS) of the corpus cavernosum may be the source of the NO, the former initiating erection, and the latter providing sustained maximal erection. The relative contribution of the different forms of NOS to erection has not been definitely established. However, more than one isoform of nNOS may be involved.

Mice lacking both eNOS and nNOS have erections, show normal mating behavior, and respond with erection to electrical stimulation of the cavernous nerves. Surprisingly, isolated corporal tissue from both wild-type and NOS-deleted animals has demonstrated similar responses to electrical stimulation. However, Hurt et al. showed that alternatively spliced forms of nNOS are major mediators of penile erection.

cGMP signals via different receptors in eukaryotic cells, including ion channels, phosphodiesterases, and protein kinases. At present, the molecular targets that are activated by cGMP in order to execute the relaxation of penile smooth muscle are not known. Two different cGMP-dependent protein kinases (cGK-I and cGK-II) have been identified in mammals. Inactivation of cGK-I in mice abolishes both NO–cGMP-dependent relaxation of vascular and intestinal smooth muscle and the inhibition of platelet aggregation, causing hypertension, intestinal dysmotility, and abnormal hemostasis. Hyun et al. suggested that lithium, by interfering with the NO pathway in both the endothelium and the nitrergic nerves, can result in impairment of both the endothelium- and NANC-mediated relaxation of rat corpus cavernosum. Male cGK-I-deficient mice seem to have very low reproductive capability, probably owing to the markedly reduced ability of their corpus cavernosum tissues to relax in response to NO, whether it is neuronally or endothelially released or exogenously administered. Analysis of the NO–cGMP-induced relaxation clearly shows that cGK-I is the major mediator of the cGMP signaling cascade in murine corpus cavernosum tissue. Its absence cannot be compensated for by the cAMP signaling cascade. Taken together, these findings suggest that activation of cGK-I is a key step in the signal cascade leading to penile erection.

Bivalacqua et al. investigated the expression of cGMP-dependent protein kinase (PKG)-1-alpha and PKG-1-beta in the corpus cavernosum and evaluated the effect of adenoviral gene transfer of PKG-1-alpha to the erectile compartment on erectile function in a rat model of diabetes. They found PKG-1-alpha and PKG-1-beta activities to be reduced in the erectile tissue of the diabetic rat. Gene transfer of PKG-1-alpha to the penis restored PKG activity and erectile function in vivo in diabetic rats. They concluded that gene therapy procedures targeting PKG-1-alpha might be an interesting future therapeutic approach to overcoming diabetic ED resistant to oral pharmacotherapy.

Angulo et al. evaluated the influence of protein kinase C (PKC) activity on penile smooth muscle tone in tissues from diabetic and non-diabetic men with ED. They found that overactivity of PKC in diabetes is responsible for enhanced contraction and reduced endothelium-dependent relaxation of human corpus cavernosum smooth muscle. Thus, the authors concluded that such alterations can result in ED.

Vasoactive intestinal polypeptide and vasoactive intestinal polypeptide receptors

Mammalian penises are richly supplied with nerves containing vasoactive intestinal polypeptide (VIP). The majority of
these nerves also contain immunoreactivity to NOS, and co-localization of NOS and VIP within nerves innervating the penis of both animals and humans has been demonstrated by many investigators. It seems that most of these NO- and VIP-containing neurons are cholinergic, since they also contain vesicular acetylcholine transporter (VACHT), which is a specific marker for cholinergic neurons. VIP receptors (types 1 and 2), linked via a stimulatory G protein to adenyl cyclase, are considered to mediate the actions of the peptide. The importance of the different subtypes of VIP in penile tissues has not been clarified. VIP-related peptides (such as pituitary adenyl cyclase-activating peptide (PACAP), which has been found to be co-localized with VIP in penile nerves), seem to act through one of the VIP receptors. The stimulatory effect of VIP on adenyl cyclase leads to an increase in cAMP, which in turn activates CAMP-dependent protein kinase.

Undeniably, VIP has both an inhibitory and relaxing effect on strips of human corpus cavernosum tissue and cavernosal vessels in vitro, but it has been difficult to show convincingly that VIP released from nerves is responsible for relaxation of penile smooth muscle in vitro or in vivo. Thus, the role of VIP as a neurotransmitter or modulator of neurotransmission in the penis has not been established. Even if its physiological role in penile erection and in ED remains to be settled, VIP receptors in the penis are an interesting therapeutic target.

Prostanoids and prostanoid receptors

Human corpus cavernosum tissue has the ability to synthesize various prostanoids, and it has the additional ability to metabolize them locally. The production of prostanoids can be modulated by oxygen tension, and it is suppressed by hypoxia. Corresponding to the five primary active prostanoid metabolites [prostaglandin (PG) D-2, PGE-2, PGF-2, PGI-2, and thromboxane A2 (TXA2)], there are five major groups of receptors that mediate their effects (the DP, EP, FP, IP, and TP receptors). cDNAs encoding representatives of each of these groups of receptors have been cloned, including several subtypes of EP receptors.

Penile tissues may contain most of these groups of receptors; however, their role in penile physiology is still far from established. Prostanoids may be involved in contraction of erectile tissues via PGF-2α and TXA2 stimulating thromboxane (TX) and FP receptors and initiating phosphoinositide turnover, as well as in relaxation via PGE-1 and PGE-2, stimulating EP receptors (EP2–EP4) and initiating an increase in the intracellular concentration of cAMP. Prostanoids may also be involved in the inhibition of platelet aggregation and white cell adhesion, and recent data suggest that prostanoids and transforming growth factor (TGF)-beta-1 may have a role in the modulation of collagen synthesis and in the regulation of fibrosis of the corpus cavernosum.

Dopamine and dopamine receptors

Hyun et al. found dopamine D1 and D2 receptor gene expression in rat corpora cavernosa. In situ hybridization signals for dopamine D1 and D2 receptor mRNAs were localized to corpus cavernosal tissues and dorsal vessels in the rat penis, and Western blot analyses confirmed the presence of dopamine D1 and D2 receptor proteins. Immunohistochemically, peripheral dopamine D1 and D2 receptor proteins were detected in dorsal nerves, dorsal vessels, and corpus cavernosal smooth muscle. d’Emmanuelle di Villa Bianca demonstrated that both D1 and D2 receptors were expressed in the human corpus cavernosum, D1 receptors being two-fold more abundant than D2 receptors, and that both receptors were mainly localized on the smooth muscle cell component. They concluded that apomorphine had a peripheral relaxant direct effect, as well as an anti-adrenergic activity, and that human corpus cavernosum possessed more D1-like receptors (D1 and D5) than D2-like receptors (D2, D3 and D4). Both D1- and D2-like receptors were mainly localized on smooth muscle cells, and the relaxant activity was most probably mediated by D1-like receptors, partially through NO release from endothelium.

Apomorphine may thus not only amplify sexual and copulatory behavior but also, by a complementary role, amplify neurogenically mediated erections by acting in the periphery. On the other hand, Matsumoto et al. investigated the role of peripheral dopamine receptors for regulation of penile erection. They found that in isolated corpus cavernosum from rats, pre- and postjunctional effects of apomorphine appeared to involve dopamine D1- and D2-like receptors, as well as alpha-adrenoceptors. At relevant systemic doses of apomorphine, however, peripheral effects of the compound were unlikely to contribute to its proerectile effects in rats.

Serotonin and serotonin receptors

Peripheral serotonin (5-HT) receptors have been suggested as participating in the control of penile flaccidity and detumescence, but their importance has not been definitively established. Studies in animals (rats and rabbits) suggested involvement of 5-HT-1A, 5-HT-1B, and 5-HT-2A receptors. In the human corpus cavernosum the presence of 5-HT-4 receptors was reported by Hayes et al., and Uckert et al. demonstrated 5-HT-1A-mediated contractions in this tissue. Further studies by Lau et al. confirmed these findings, and it was suggested that 5-HT may play a role in the human detumescence process, via 5-HT-1A, 5-HT-2A, and 5-HT-4 receptors.

Endocannabinoids

Little information exists concerning the peripheral effect of cannabinoids on corpus cavernosum tissue. Ghasemi et al. investigated the effect of the endogenous cannabinoid, anandamide, on the NANC relaxant responses to electrical field stimulation in isolated rat corpus cavernosum. They showed that anandamide has a potentiating effect on NANC-mediated relaxation of rat corpus cavernosum through both cannabinoid receptor type 1 (CB1) and vanilloid receptors. Furthermore, they demonstrated that the NO-mediated component of the NANC relaxant responses to electrical stimulation is involved in this enhancement. The same group studied the effect of biliary cirrhosis on NANC-mediated relaxation of rat corpus cavernosum and the possible roles of endocannabinoid and NO systems in this model. NANC-mediated relaxation was enhanced in corporal strips from cirrhotic animals.
Anandamide potentiated the relaxations in both groups, AM251 (a CB1 receptor antagonist) and capsazepine (a vanilloid TRPV1 receptor antagonist), but not AM630 (a CB2 receptor antagonist), prevented the enhanced relaxations of cirrhotic strips. The non-selective NOS inhibitor 1-NAME and the selective neuronal NOS inhibitor L-NPA inhibited relaxations in both groups, but cirrhotic groups were more resistant to the inhibitory effects of these agents. Relaxations to sodium nitroprusside (NO donor) were similar in tissues from the two groups. The authors concluded that cirrhosis potentiates the neurogenic relaxation of rat corpus cavernosum, probably via the NO pathway and involving cannabinoid CB1 and vanilloid receptors.

Western blot experiments revealed the presence of both CB1 and CB2 receptors at specific bands. CB1- and CB2-immunoreactivity (1-IR) was found in nerve fibers within and between strands of corporal smooth muscle. CB1- and CB2-IR nerves also expressed immunoreactivity for NOS and TRPV1. In contrast, neither CB1 nor CB2 nerves were co-localized with calcitonin gene related peptide (CGRP)– or tyrosine hydroxylase (TH)–containing nerves.

Anandamide (10−3 to 10−4 M) had no direct contractile effects on corporal smooth muscle, no relaxant effects on precontracted preparations, and no significant effect on phenylephrine-induced contractions. However, anandamide inhibited electrically evoked smooth muscle relaxations at 10 μM and 100 μM (p = 0.01). Further studies are needed to establish the role of the endocannabinoid system in erectile tissue.

The RhoA–Rho-kinase pathway

A major mechanism of the calcium sensitization of smooth muscle contraction is through the inhibition of the smooth muscle myosin phosphatase (MLCP). The resulting myosin phosphorylation and subsequent smooth muscle contraction therefore occurs without a change in sarcoplasmic calcium concentration. Several studies have revealed important roles for the small GTPase, RhoA, and its effector, Rho-associated kinase (or Rho-kinase) in calcium-independent regulation of smooth muscle contraction. The RhoA–Rho-kinase pathway modulates the level of phosphorylation of the myosin light chain of myosin II, mainly through inhibition of myosin phosphatase. This calcium-sensitizing RhoA–Rho-kinase pathway may also play a synergistic role in cavernosal vasoconstriction to maintain penile flaccidity. Rho-kinase is known to inhibit myosin light chain phosphatase and to directly phosphorylate myosin light chains, resulting in a net increase in activated myosin and the promotion of cellular contraction. Although Rho-kinase protein and mRNA have been detected in cavernosal tissue, the role of Rho-kinase in the regulation of cavernosal tone is not established. Using the Rho-kinase antagonist Y-27632, Chitaley et al. examined the role of Rho-kinase in cavernosal tone, based on the hypothesis that antagonism of Rho-kinase results in increased corpus cavernosum pressure, initiating the erectile response independently of NO. They found that Rho-kinase antagonism stimulated rat penile erection independently of NO, and suggested that this principle could be a potential alternative avenue for the treatment of ED.

Since RhoA–Rho-kinase-mediated calcium sensitization is important for regulation of smooth muscle contraction, increased RhoA–Rho-kinase activity may lead to abnormal contractility of the corpora cavernosa. Evidence has been presented that elevated RhoA–Rho-kinase activity contributes to the pathogenesis of diseases such as diabetes and hypertension, and possibly to other conditions associated with ED, such as hypogonadism and aging. Several studies have suggested that NO inhibits RhoA–Rho-kinase activity, but the detailed mechanisms by which this regulation occurs are yet to be determined.

Vignozzi et al. investigated the effect of testosterone on the RhoA–ROCK (Rho-kinase) signaling in diabetes. The authors found that over-expression of RhoA–ROCK signaling contributes to diabetes-related ED. Moreover, treating hypogonadism in the course of diabetes may maintain erectile function also by normalizing RhoA–ROCK pathway upregulation.

Theoretically, suppression of an increased RhoA–Rho-kinase activity is an attractive therapeutic principle in ED. However, the ubiquitous occurrence of the Rho–Rho-kinase pathway limits the use of Rho-kinase inhibitors. If regulators of RhoA–Rho-kinase uniquely expressed in penile tissue can be demonstrated, they may be targets for drugs. This will potentially lead to the development of new therapeutic agents for the treatment of ED.

Demir et al. investigated the relationship of adrenergic responses in corpus cavernosum tissues in the presence of bladder outlet obstruction using the alpha-1AR receptor antagonist doxazosin and the Rho-kinase inhibitor Y-27632. The contractility of human corpus cavernosum was increased in the presence of bladder outlet obstruction; doxazosin and Y-27632 generated effective corpus cavernosum smooth muscle relaxation in the presence of obstruction. Doxazosin and Y-27632 may therefore be the alternatives for the treatment of ED associated with benign prostatic hyperplasia.

Sex hormones

The peripheral effects of sex hormones on penile smooth muscle have not been established. Penile erectile tissue from patients undergoing sex reassignment operations after estrogen treatment has been used in several studies, including those focusing on receptor-mediated responses in human corpus cavernosum tissue. It has been claimed that hormonal treatment does not qualitatively change responses to drugs and electrical field stimulation. However, this is still open to discussion, since systematic comparisons between tissues from these patient groups and normal subjects have not been performed.

In vivo studies of castrated dogs suggest that androgen deficiency has direct effects on the function of the erectile tissues, resulting in a higher tone of the detumescence factors than could be explained by an incomplete relaxation of the trabecular smooth muscle. In isolated human corpus cavernosum pre-treated with testosterone for 30 minutes, testosterone appeared to have no effect on contraction or relaxation. On the other hand, castration enhanced NANC nerve-mediated relaxation in corpus cavernosum tissue from rabbits. Since the response to the NO donor morpholino-sydnonimine was the same in corpus cavernosum tissue from
controls and castrated animals, it may be assumed that the responsiveness of the penile erectile tissue to NO was not changed. In castrated animals, however, there was a reduction in the release of norepinephrine from adrenergic nerves caused by electrical stimulation. The hormonal changes caused by castration, which include a change in the balance between androgens and estrogens, may additionally stimulate the synthesis or release of NO. The influence of androgens on erectile function may be mediated by the NO–cGMP pathway to a significant extent, even though non-NO-dependent pathways may have been demonstrated.

The effects of castration and testosterone replacement on peripheral autonomic control of penile erection have been studied in dogs and rats. The findings in the dog study suggest that castration and the resulting low plasma testosterone levels did not directly affect penile erectile ability through actions on peripheral nerves or corpora cavernosa. In the rat study, it was shown that castration reduced the erectile response, and that testosterone could restore it. It was concluded from these experiments, which included preganglionic anatomy of the pelvic nerves, that testosterone enhances the erectile response to cavernous nerve stimulation acting peripherally to the spinal cord, with proerectile postganglionic parasympathetic neurons as the hormonal target.

A rat study evaluated whether testosterone deprivation affects axonal regeneration in cavernous nerve grafts or the erectile response to cavernous nerve graft stimulation. Sprague–Dawley rats underwent bilateral cavernous nerve neurotomy, followed by unilateral nerve graft using the genitofemoral nerve. Rats were then randomized to three groups: castrated, intact, and testosterone-treated. At 3 months grafts were explored and electrostimulation was performed, with responses in terms of intracavernous pressure recorded. Grafted nerves were then harvested for immunohistochemical analysis. There was a significant difference in the maximal intracavernosal pressure response between groups. Total axon counts did not differ between treatment groups. Castrated animals had lower nNOS axon counts than intact animals. The authors concluded that castration resulted in a decreased erectile response to electrostimulation following nerve grafting. This may be due to decreased graft nNOS-positive axonal regeneration, and it may have important implications in patients in whom cavernous nerve grafting could be considered.

Androgens may regulate the alpha-AR responsiveness of cavernous smooth muscle. Compared with normal rats, castrated animals showed an enhanced reactivity to alpha-1-AR stimulation. Androgens may also have important functions in the intrapenile mechanisms of erection. In the penis, androgen deprivation leads to smooth muscle cell apoptosis, a relative increase in connective tissue content, and a consequently reduced relaxation of the erectile tissue.

Conclusion

The central regulation of the erectile process is still only partly known. Central transmitter systems, which seem to be dependent on androgens as well as NO, may be the targets of future drugs aimed at the treatment of ED. In penile erectile tissues, the different steps involved in neurotransmission, impulse propagation, and intracellular transduction of neural signals require further investigation. Increased knowledge of the central and peripheral changes associated with ED may lead to an increased understanding of these pathogenetic mechanisms and therefore to new treatments and possibly even to prevention of the disorder.

REFERENCES


Receptor pharmacology related to erectile dysfunction


Environmental erectile dysfunction

Arthur L Burnett

Introduction

In the course of recent medical advances brought to the clinical management of erectile dysfunction (ED) in recent years, such as highly publicized effective oral pharmacotherapy for the condition, additional emphasis has now been given to its public health significance. Epidemiologic studies have established reasonably well the high frequency of ED presently worldwide, despite variations in diagnostic definitions of the disorder. Overall prevalence rates of ED range between 10% and 20%, with the majority of studies reporting an overall rate closer to 20%.\(^\text{1}\) Although incidence data for the disorder are scant, estimates approach 26 cases per 1,000 men annually, according to the longitudinal analysis of the often-quoted Massachusetts Male Aging Study (MMAS) representing men 40–69 years of age.\(^\text{2}\) Further, a longitudinal study of placebo-treated men in the Prostate Cancer Prevention Trial who were 55 years or older found an incident ED rate of 57% at 5 years and 65% at 7 years.\(^\text{3}\)

Such studies have also served to enumerate primary risk factors for ED, which have an impact on frequency rates.\(^\text{4-6}\) Aging, diabetes, cardiovascular disorders, hypertension, dyslipidemia, obesity, cigarette smoking, and prostate disorders all show positive relationships with the occurrence of the disorder. Frequency estimates are further impacted by the severity and duration of associated risk factors. Ongoing scientific investigations are useful to define the biological basis and the extent to which highly prevalent medical conditions and other risk factors adversely affect the physiology and molecular mechanisms of penile erection. The public health emphasis associated with ED also affords societal prevention opportunities to develop and implement programs to lessen its occurrence. Indeed, observational and intervention studies have begun to explore the extent to which ED risk factors are modifiable, with subsequent improvement in health outcomes and quality of sexual life.\(^\text{7-10}\)

A growing interest in the field along the lines of identifying at-risk populations and specific risk factors for ED pertains to environmental exposures to toxicants or other unhealthful substances. Precisely, it may be hypothesized that deleterious exposure to chemical and physical agents generated and released into a person’s surroundings constitutes a risk factor for developing ED. The proposal is far from implausible, and the notion of environmental exposure risks mimics widespread concerns of possibly adverse health effects of cigarette smoking and alcohol consumption on erectile function (see recent reports of the United States Surgeon General and the Board of Science and Education and Tobacco Control Resource Centre of the British Medical Association).\(^\text{11,12}\) The idea that environmental exposures may represent a risk factor for ED borrows from concepts that were developed in the field of male reproductive function that suggested that certain pesticides, solvents, and related chemical agents may affect fertility.\(^\text{13-16}\) Additionally, early citations in the medical literature have documented men reporting ED whose occupations included agricultural and industrial work.\(^\text{13,14,17,18}\)

The intent of this chapter is both to evaluate the currently available observational and experimental data linking environmental and occupational exposures with the development of ED and to determine pathophysiologic concepts in support of this link. This exercise also explores whether environmental exposures should be assigned merely an association with ED or whether these possibly represent a cause for this disorder. Accordingly, the evaluation aptly applies rigorous causality criteria as proposed by the First US Surgeon General’s Advisory Committee on Smoking and Health in 1964.\(^\text{19}\) Several criteria to be considered with respect to a causal association include consistency, specificity, strength, temporality, and coherence.\(^\text{20}\) Consistency is met by repeated studies that examine different clinical settings, subjects, eligibility criteria, and exposure opportunities. Specificity refers to a dose–response effect with an assessment that establishes independence of a potential risk variable. Strength identifies the relative risk estimation. Temporality implies that the effect occurs with the onset of the exposure and, supposedly, the effect is diminished with cessation of the exposure. Coherence means that a biological mechanism has been explored and found to be tenable. Satisfaction of these criteria would strongly support the proposal that environmental exposures qualify as a causal basis for ED.

Biologic basis for exposure risks

A major consideration in advancing the current proposal is the extent to which a biological basis can be offered to explain the possible harm of environmental exposures on erectile function. In this regard, it would be important to determine whether plausible biological mechanisms can be formulated in support of this premise, in accordance with how chemical and physical agents feasibly disturb erection
regulatory determinants or physiologic processes of the erectile response.

Current lines of thought suggest that environmental toxicants exert a principal effect by deranging endogenous hormones involved in reproductive and sexual function. The majority of environmental toxicology studies have centered on the threat of various compounds on male reproductive health, homeostasis, and physical development.\textsuperscript{15-16} These compounds have been collectively termed 'endocrine disrupters' as defined by the United States Environmental Protection Agency.\textsuperscript{21} They include pesticides (e.g. 2,4-dichlorophenoxyacetic acid (2,4-D), dichlorodiphenyl trichloroethane (DDT), dieldrin), plasticizers (e.g. styrene, phenols, and phthalates), and industrial chemicals [e.g. polychlorinated biphenyls (PCBs) and dioxins].\textsuperscript{22-24} In light of the documented anti-androgenic or estrogenic properties of many of these environmental chemicals, it is conceivable that they have a negative impact on erectile function. This contention is consistent with accumulating evidence that erectile function is a hormone-dependent process. Various lines of evidence indicate that androgens are involved in maintaining the responsiveness of penile vascular smooth muscle to sexual stimuli, priming erection regulatory factors such as signaling by the erection mediator nitric oxide (NO), and optimizing function of central neuronal nuclei responsible for penile erection.\textsuperscript{25-27}

Alternative proposals have centered on possible effects of environmental chemicals as neurotoxins and the plausibility that these could impair the neurogenic basis of penile erection. Studies from the 1950s and 1960s have shown that various compounds (e.g. di-isopropyl fluorophosphates, organophosphorus insecticides) produce toxic effects by inhibiting cholinesterase and acetylcholinesterase activity, thereby causing an accumulation of acetylcholine and eventually persistent depolarization at cholinergic nerve endings.\textsuperscript{28,29} Contributions of the cholinergic system at either central or peripheral levels to the regulation of penile erection would conceivably then be potentially compromised by environmental toxicant exposure. It would be presumptuous at this time to imply that such exposure directly affects the neurally based NO signal transduction pathway, which operates as the predominant neuroregulatory control system for penile erection.\textsuperscript{30}

These circumstances introduce the possibility of information bias, possibly toward underestimating the effects of the environmental exposure. Some studies have applied external indicators (e.g. known location and duration of exposure) in an effort to state the exposure risk, although the exact exposure conditions (i.e. the intensity and frequency of exposure) are generally elusive. With respect to erectile function assessment, a single-item assessment (e.g. 'Do you experience difficulty getting or maintaining an erection that is rigid enough for satisfactory sexual intercourse?') has gained prominence, particularly for population-based epidemiologic studies.\textsuperscript{31} This brief manner of data collection may also introduce the possibility of information bias, probably toward under-reporting. In addition, it frequently does not reveal the severity of the erectile impairment. However, the findings usually provide insight into the probable significance of the problem within the general population.

Case series
Several descriptions of a link between environmental exposure and ED qualify as observational case series. As such, they are limited by not having true comparison groups. With expectations that increasingly formal studies will emerge that may provide more robust data, these reports are nonetheless informative.

With a report published in 1970, Espir et al. may be credited with first bringing attention to the matter of environmental chemicals potentially affecting erectile function.\textsuperscript{32} These investigators observed that four farm workers in the UK who had been using herbicides and pesticides in intensive agriculture over a 1-year interval lost erectile ability. Organophosphorus chemicals were implicated as the environmental exposure, and disruption of testosterone metabolism was inferred.\textsuperscript{32} Upon discontinuing working with the chemicals, all men recovered erectile function.

Oliva et al. studied the ED risk associated with chemical and physical environmental agents in men located in a highly agricultural and industrial region of Argentina who sought medical attention for their erectile impairment.\textsuperscript{33} The investigators determined that 28% of the 199 men were exposed to pesticides or to solvents, with median exposure times of 12 years or 14 years, respectively. Confounding lifestyle and medical risk factors for ED were noted in this population, including cigarette smoking (in 31%), alcohol abuse (in 33%), diabetes (in 11%), hypertension (in 34%), cardiovascular diseases (in 16%), and therapeutic drugs (in 22%).

In a single case report, Park et al. associated chronic exposure to methyl bromide with ED.\textsuperscript{34} The patient, who had been working in the fumigation department at a public food quarantine station for 12 years, was confirmed to manifest a peripheral sensorimotor polineuropathy, consistent with the known neurotoxicity associated with this fumigant. Upon discontinuing his job, his recovery of spontaneous erectile function was minimal.

Population-based studies
More valid appraisals of the effects of environmental toxicants on erectile function have been obtained through

Epidemiologic evidence

Observational data
In exploring the association between environmental exposure and the occurrence of ED, as for many epidemiologic studies attempting to link a health risk factor and impaired sexual function, some consideration should be given to ascertaining observational data. For this analysis, self-reporting and application of other subjective instruments (e.g. logs, questionnaires, and sexual function inventories), rather than objective, quantitative measurements, were commonly used to determine substance exposure and erectile performance. A special concern associated with documenting environmental exposure subjectively is the difficulty in recording exposure level (i.e. the dosage effect), which is generally derived retrospectively and may also not be accurately identified by the person at risk.
cross-sectional, random surveys of a sample population. Several levels of investigation into the widely ranging occupational hazards of chemical compounds on reproductive and sexual functions have been undertaken. One early study focused on the effects on reproductive ability of long-term occupational exposure to lead. Lancranjan et al. carried out a comprehensive clinical and toxicological assessment of 100 workmen who had a mean occupational exposure of 8.5 years (range: 1–23 years) working at a storage battery plant in Bucharest as well as 50 technicians and office workers of this plant who worked in annex workrooms in a lead-polluted environment for a mean of 6 years (range: 1–27 years). In the course of evaluating the fertility of these men, the investigators assessed that, by sexual history, there was a high rate of ‘pathologic erections’ in the lead-exposed workmen (33%) compared with that of their coworkers (14%), who were verified to have a physiologic, non-toxic absorption of lead.

This approach to the evaluation of environmental occupational risk on reproductive ability was similarly undertaken in the USA by the National Institute for Occupational Safety and Health (NIOSH). Under such auspices, Landrigan et al. described the risk of ED among 39 randomly selected male chemical workers employed at a large manufacturing plant in Alabama in 1981 who were exposed to the stilbene derivative 4,4′-diaminostilbene-2,2′-disulfonic acid (DAS), a chemical used in the production of optical brightening agents. By interview, 14 (36%) of these workers were identified as experiencing ED, and 8 (29%) of 28 exposed workers who underwent hormonal evaluation were found to have reduced serum testosterone measurements (less than 300 mg/ml). The latter finding suggested to the investigators that the adverse health effects may have been associated with the estrogenic activity of the chemical.

The official report released by NIOSH in the USA in 1990, known as The Health Hazard Evaluation, comprised a formal questionnaire survey conducted during 1981–1983 among men working in the area of the aforementioned chemical plant that manufactured DAS. Among 44 men aged 20–57 years comprising the study population, 11 (25%) reported current or previous ED that developed after beginning work (and over an average length of employment of 4.7 years). Low levels of serum testosterone (less than 350 ng/dl) were found in 16 (37%) of the men. The second report of the NIOSH Health Hazard Evaluation, which was a questionnaire-based survey conducted in 1991, compared self-reported sexual function in 30 male workers who were currently manufacturing DAS, 20 former DAS workers, and 35 workers who manufactured plastics additives in a different manufacturing area (unexposed workers). Adjusting for age, currently exposed workers were more likely than unexposed workers to score in the lowest quartile for ‘physiologic competence’ (a measure of erection ability) (adjusted odds ratio 1.9; 95% CI 0.6–6.4) and ‘activity–performance factor II’ (a measure of ejaculatory function) (adjusted odds ratio 5.8; 95% CI 1.3–27.3). Currently exposed workers were also more likely than unexposed workers to score in the lowest quartile for ‘sexual interest’ (adjusted odds ratio 1.9; 95% CI 0.5–7.2). Former DAS workers reported problems associated with ‘activity–performance factors I and II’ (measures of quality of erection and ejaculatory function, respectively) (adjusted odds ratio 2.2; 95% CI 0.5–10.1 and adjusted odds ratio 6.7; 95% CI 1.2–35.9, respectively) compared with unexposed workers.

Sexual dysfunction observed in male viscose rayon factory workers in Belgium were speculated to be the result of their potentially toxic exposure to carbon disulfide, which is standardly used in this industry, and it prompted an epidemiologic investigation. In their questionnaire-based study, Vanhoorne et al. found that the complaint of ED was registered at a frequency rate of 15.7% (18 of 116 men) among exposed workers, representing a significantly greater occurrence than the rate of 3.8% (3 of 79 men) found in non-exposed workers.

Additional studies support the direct association between pesticide exposure and ED. Amr et al. conducted an epidemiologic investigation in Egypt to determine whether pesticides frequently used in the agricultural region (e.g. carbamates, pyrethroids, and organophosphates) exert adverse effects on erectile function. The study population consisted of randomly selected workers – 208 pesticide formulators and 172 pesticide applicators – whose responses to standardized health questionnaires were compared with that of 223 unexposed control subjects (72 from an urban textile factory, who were matched with the pesticide formulators, and 151 from a rural area, who were matched with the pesticide applicators), who were otherwise matched for age and socioeconomic and educational levels. The formulators were directly exposed to pesticides for at least 40 hours per week for at least 9 months of the year for at least 2 consecutive years, and the applicators were exposed for at least 2 consecutive years during standard farm work. ED was significantly more frequent in the exposed group (the pesticide formulators) than in the unexposed control group, 26.9% vs 4.2% (p < 0.001). Both the pesticide formulators and the applicators demonstrated a significantly greater frequency of psychiatric disorders than the control group.

Disease correlates

It is surmised that several relationships between environmental exposure and ED risk can be characterized, which may contribute toward affirming the risk association. Type of exposure, dose–response effect, the effect of risk factor covariates, and the effects of discontinuation of exposure represent such disease correlates. From the aforementioned section, it would appear that various types of environmental exposure correlate with ED. Passive exposure to cigarette smoke, which contains numerous pollutants, represents a further example of a type of environmental exposure that has been shown to be a risk factor for ED. According to a prospective analysis of the Massachusetts Male Aging Study, the odds of incident ED were more than doubled in people exposed to passive cigarette smoke, if present both at home and at work, compared with the odds in unexposed people (adjusted odds ratio 2.07; 95% CI 1.04–4.13, p = 0.04). In contrast, passive exposure at home or at work alone did not increase the odds of incident ED in non-smokers, but each increment of exposure did increase the estimated likelihood of ED in smokers. A similar analysis resulted from the Boston Area Community Health survey, which determined that men passively exposed to cigarette smoke had a moderate, statistically non-significant increase in
ED (adjusted odds ratio 1.33; 95% CI 0.69–2.55) compared with those who had never smoked and had not been exposed to passive smoking.49

The relationship between the amount of exposure to an environmental toxicant and the extent of ED would describe a dose–response effect. Support for this concept is provided in the literature. Among 150 men with lead exposure categorized as being ‘poisoned’ or having ‘moderate’ absorption, ‘slight’ absorption, and ‘physiologic’ absorption, rates of ‘pathologic erections’ were 48%, 33%, 22%, and 14%, respectively.11 Among viscous rayon workers, those who were chemically exposed to carbon disulfide with a high cumulative exposure index score (amount and duration of exposure >300 mg/m³ years) manifested a significantly higher ED rate (20%) than that (9.1%) for men with a low cumulative index score (>300 mg/m³ years).37 In a similar way, a direct correlation between duration of exposure and frequency of ED was found among Egyptian pesticide formulators.38 For exposure durations of ≤5 years, ≤10 years, ≥15 years, and ≥20 years, ED rates were 12.2%, 17.8%, 35%, and 35.8%, respectively, with statistically significant differences shown for the two longer durations compared with the shorter durations. In another study, which applied a logistic regression analysis and a reference group of men with normal erectile function to calculate strength of association, objectively confirmed ED was found to be greater in men who were frequently exposed to pesticides (odds ratio 8.4) than in men who were so exposed only occasionally (odds ratio 4.4).39

The premise that environmental exposure adversely affects erectile function would seemingly be strengthened by epidemiologic evidence that discontinuation of exposure permits recovery of erectile function. In support of this concept, it was shown that farm workers who developed ED after exposure to toxic chemicals recovered erectile function after discontinuing their occupations.17 On the other hand, a fumigator intoxicated by occupational methyl bromide did not recover erections after discontinuing his occupation.46 An explanation for the discrepancy follows the differences in amount of exposure in these two examples, the former consisting of 1 year of exposure and the latter consisting of 12 years of exposure; discontinuation of exposure after a significant life-time interval may fail to modify the frequency of ED. Under conditions of long-term exposure, irreversible erectile impairment may conceivably have developed.

Clinical data

It would be meaningful to evaluate a link between environmental exposure and ED based on objective criteria. The supposition is that quantitative measurements can be used to offer indices of the integrity of erectile function among people exposed to environmental toxicants.

Penile tumescence studies

Nocturnal penile tumescence (NPT) monitoring provides a non-invasive diagnostic technique to quantify erection physiology objectively during the naturally occurring cycle of sleep–related penile erections. These spontaneous episodes of tumescence normally accompany rapid eye movement (REM) sleep and are diminished in men with presumably organic ED.46 Applying NPT in a study of Argentinian agricultural and industrial workers, Oliva et al. determined that the risk of having a flat erectile pattern was significantly increased in those with pesticide exposure (odds ratio 7.1; 95% CI 1.5–33.0) and solvent exposure (odds ratio 12.2; 95% CI 1.2–124.8), with a slightly elevated risk to a non-significant degree from exposure to heat (odds ratio 1.7; 95% CI 0.3–9.4).33

Clinical toxicologic assessment

The quantitative measurement of environmental chemicals in the tissues of people suspected to be exposed to such agents who report ED offers an elegant approach to study their possible role in the etiology of ED. Such an evaluation equates to assaying for biomarkers of environmental chemical exposure. In a clinic-based case control study conducted in Kingston, Ontario, Polsky et al. explored whether organochlorines, which are related to such pollutants as polychlorinated biphenyls and chlorinated pesticides and which are measurable in blood, are associated with ED risk.41 The investigators found that plasma levels of an assortment of these compounds were no different among 101 men presenting with ED and 234 comparable control subjects, after adjusting for age, total lipids, and health condition confounders. Results from this study would imply that environmental chemicals are uninvolved in ED risk. However, the investigators conceded that, since the magnitude of the risk in the general population may be low, a study with a larger sample size may be required to detect the actual risk. The study also does not exclude the possibility that in an affected person a sufficiently toxic exposure to environmental chemicals may yet comprise a significant ED risk.

Lancranjan et al. studying the effect of lead on reproductive ability among workers in a storage battery plant in Bucharest, also evaluated the levels of toxic absorption of lead and lead metabolites in blood and urine and a basic hematologic screen along with urinary 17-ketosteroid (17-KS) levels as a measure of Leydig cell function.19 The investigators showed toxicologic abnormalities to a greater extent in pathologic lead-exposed groups with higher rates of erection difficulties in contrast with control subjects, affirming that such parameters may serve as indicators of erectile impairment in lead-exposed people. They did not find a relationship between the level of lead absorption and 17-KS elimination, which together with observed abnormal fertility parameters in lead-exposed workers led them to suggest that the likely toxic effects of the heavy metal on the body, including the testis, is exerted by mechanisms other than disrupted function of the hypothalamic–pituitary–gonadal axis.

In another clinic-based case control study performed in Cairo, Egypt, Anis et al. studied the potential for chronic lead exposure to have caused ED in 34 men presenting with the condition who were scheduled to undergo penile prosthesis surgery.42 The investigators found that 16 of the 34 patients (47%) and none of clinically matched control subjects had elevated serum levels of lead (>25g/dl). They further found that the serum lead level significantly correlated with cavernous tissue lead levels in the patient group and also observed lead granule deposition histologically in cavernous tissue removed from patients at the time of their surgeries.
Additionally, they confirmed higher serum levels of reactive oxygen species and lower levels of antioxidants, indicating the presence of oxidative stress, in people with a high serum lead level compared with those with a low serum lead level. The findings suggest that lead toxicity may serve as a risk factor for ED and probably exerts effects pathogenically by oxidative stress mechanisms.

Experimental data

Experimental studies in which controlled exposures to environmental chemicals are applied provide an additional approach to ascertain the consequences of the exposure on erectile function. Such studies commonly apply rigorous scientific methodology (e.g. random allocation of subjects to experimental and control groups, the use of different control groups, and the application of blinding procedures to reduce bias), and as such offer the most robust data from which to draw conclusions regarding risk associations. As one would suspect, such ideal studies in which environmental exposures are controllably delivered to humans are nearly impossible to conduct. An informative perspective is provided, however, when examining the results from several experiments testing the effects of cigarette smoking on erectile function in humans. These experiments, which mainly consisted of either acute exposure or exposure discontinuation study designs, showed direct temporal and dosing level effects of cigarette smoking on various erectile parameters.45-47

Animal models offer another useful approach for investigating the association between environmental chemical exposure and ED. Brien et al. studied the effects of p,p-dichlorodiphenyl dichloroethylene (p,p-DDE), a prominent and persistent metabolite of the insecticide DDT, on erectile function in a rat model of apomorphine-induced erections.48 The investigators found that animals given a single intraperitoneal dose of the chemical agent had decreased erectile function for at least 2 weeks compared with responses of control rats. However, they were able to reverse the ED in p,p-DDE-treated rats using high doses of testosterone. The investigators concluded that p,p-DDE exerts a deleterious effect on penile erection, presumably by interference with androgen-mediated mechanisms. The conclusion is consistent with the known action of this chemical agent as an androgen receptor antagonist and supports altered steroid hormone function resulting from certain chemical exposures as a proximate basis for environmental ED.

Synthesis of the evidence

Available evidence indicates that environmental chemical exposure constitutes a plausible risk factor for ED. However, the causal basis for this association must be carefully evaluated. Several criteria require consideration prior to establishing causation per se. With regard to consistency of the association, both case series and population-based studies establishing rates of ED among people exposed to various environmental chemicals provide meaningful support. Population-based studies afford a more accurate observational basis for this assessment than uncontrolled case series, although the relative dearth of these studies hampers the ability to reach a definitive conclusion.

The strength of the association also rests on limited available information at this time, although description of dose-response relationships for several exposure circumstances contributes to this line of support. Other correlates, such as temporality of the association, lend support as well, with a few observational and experimental studies demonstrating that ED follows environmental exposures and that erectile function is recoverable after the offending exposure is removed. However, observational findings do indicate the likelihood that erection recovery after exposure removal occurs appreciably only after a limited extent of life-time exposure.

Coherence of the association largely derives from experimental studies, which have tested for plausible mechanisms for the deleterious effects of environmental chemicals on erectile function. Leading possibilities in this regard include hormonal derangements and neurotoxicity. However, the exact mechanisms for erectile impairment remain unclear, and much more biomedical research will be required to advance concepts in this area.

It is acknowledged that confounding issues could hinder assessments of causation in this field of study. One concern pertaining to population-based studies is whether a potentially toxic exposure is so pervasive in a certain community of interest that it produces a magnitude of risk that is artifactsually increased. This difficulty describes prevalence bias. The assignment of risk for a certain chemical exposure at a public health level would require the study of a sufficiently large population base with appropriate control groups. As a related concern, associated with such epidemiologic studies, a particular exposure may introduce consequences that secondarily affect penile erection. Such an example of misattribution would be that of chemically exposed workers who experience psychological and general health ill-effects that subsequently interfere with sexual interest and activity. Use of validated questionnaires specific for erection ability may serve optimally to evaluate environmental exposures as a primary risk factor.

Conclusion

This analysis of clinical epidemiologic and biomedical scientific studies examining the association between environmental exposures and ED offers several conclusions. There is enough intriguing information to raise the possibility of environmental exposures as a risk factor for ED. However, it is acknowledged that limited information has been produced thus far in this field of study. At this time, it seems reasonable to suggest that environmental chemical exposures may have a negative impact on erectile function. However, the scope of evidence is presently insufficient to prove direct causal associations in many instances, and further scientific investigation is needed. It will be necessary to conduct additional observational studies with rigorous outcome assessments, along with corroborative basic scientific studies delineating biological mechanisms for the risk association. In the mean time, current information appropriately raises awareness of the potential risk and supports prudent recommendations to limit exposures to reduce possible morbidity.
14 Erectile dysfunction and treatment of carcinoma of the prostate

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Introduction

Prostate cancer is the most common non-skin cancer in American men and is the second leading cause of cancer deaths. As many as 230,000 American men were diagnosed with prostate cancer in 2007 and almost 30,000 die of the disease annually. Treatments for this universally feared malignancy include radical surgery, radiation therapy, and medical therapy. All these therapeutic alternatives can result in disorders of continence and in erectile dysfunction (ED) – decreasing the ability to obtain and maintain an erection satisfactory for vaginal penetration – which have a profound impact on men’s quality of life. Because men diagnosed with prostate cancer are often over age 50, prostate cancer and its treatment are compounded by other risk factors for ED. Men from 50 to 70 years of age have progressive increases in prostate cancer incidence and prevalence with each decade, associated with a doubling in incidence of ED from aging and other independent risk factors.1

Treatment of carcinoma of the prostate affects both vascular and neurologic supply to the penis, which, with the addition of increased vascular and psychological risk factors, increases the risk of ED. With the improvement in surgical techniques and the advent of refined nerve-sparing prostatectomy in open, laparoscopic, and robotic-assisted prostatectomy, significant preservation of erectile function can be accomplished in comparison with the older, non-nerve-sparing techniques. Despite these refinements, however, there is a significant prevalence of ED following even the best bilateral nerve-sparing radical prostatectomy. Other treatment modalities, including external beam radiation therapy, brachytherapy, cryotherapy, high-intensity focused ultrasound (HIFU), and androgen deprivation therapy, are also associated with ED.

Etiology of erectile dysfunction following treatment of prostate cancer

Because radical prostatectomy continues to be the gold standard for the treatment of organ-confined prostatic carcinoma, the majority of investigations, reports, and outcomes have been reported with surgery for the treatment of prostate cancer. Because the prevalence of pre-existing ED in men over the age of 50 is as high as 50%, even the best nerve and vascular preservation may be associated with ED. The most important apparent treatment risk is damage to the cavernosal nerves, avoided by surgical procedures employing the `nerve-sparing approach’. Nerve-sparing radical prostatectomy was first reported by Walsh et al. in 1982, and over the past 20 years it has been adopted by urologic surgeons throughout the world.2

Preserving the neurovascular bundles posterolateral to the prostatic capsule saves the innervation of the corpus cavernosum smooth muscle. Described anatomically by Walsh and Donker in 1982, this anatomic radical prostatectomy demonstrated significant improvements in erectile function following careful nerve-sparing surgery.3 Quinlan et al. reported the first results of a nerve-sparing approach, with more than 90% preserved erectile function in men under the age of 50 and 25% in men over 70.4

The etiology of ED following prostate cancer therapy, whether surgical or non-surgical, includes organic and psychogenic causes. The impact of prostate cancer on the patient and his partner are significant. The diagnosis of a frequently fatal disease produces significant anxiety and depression amongst both the patient and his family.5,6 Organic causes of ED include not only neurologic injury, but also arterial insufficiency, veno-occlusive dysfunction, and anatomic structural changes of the penis. Patients treated with androgen deprivation therapy during radiation therapy or independently will also have significant hormonal etiology for their ED.

Basic science research has demonstrated significant changes in the corpus cavernosum after denervation of the prostate. User et al. have documented significant changes in corpus cavernosum wet weight as well as mRNA content of corpus cavernosum smooth muscle tissue as early as 7 days after denervation.7 Progression of these changes continued throughout the 60 days of their study, and were significantly different from the situation in control animals. Thus denervation may produce immediate, long-lasting, and even permanent changes in the ability of the corpus cavernosum. Electron microscopy in these same animals demonstrated substantial apoptosis of perivascular and cavernosal smooth muscle and destruction of intracavernosal endothelial cells. These changes, similar to those seen with high cholesterol diets and other vascular risk factors to the corpus cavernosum, demonstrate acceleration of destruction of the vascular and endothelial cell component of the corpus cavernosum.7 In a corpus cavernosum biopsy study of men 6 months after radical prostatectomy, Schwartz et al.
have demonstrated an increase in fibrotic tissue in the corpus cavernosum and a relative decrease in smooth muscle content. In their small study, prophylactic treatment with high-dose sildenafil was able to reverse the trend of increasing cavernosal smooth muscle fibrosis.

Despite the overwhelming evidence that nerve injury produces ED following radical prostatectomy, there are other causes of ED from the surgical procedure. Nehra et al. in 1997 reported significant numbers of accessory pudendal arteries surrounding the prostate in 35% of men undergoing nerve-sparing radical prostatectomy. In this study, 50% of the men with accessory pudendal arteries had left-sided, 25% had right-sided, and 25% had bilateral accessory pudendal arteries. In many of the patients studied, these accessory pudendal arteries were the principal if not sole blood supply to the corpora cavernosa. Mulhall and Graydon in 1996 reported vasculogenic causes of ED in a group of men undergoing bilateral nerve-sparing radical prostatectomy. They were studied with penile Doppler studies and dynamic infusion cavernosography and cavernosometry (DICC). Of these 10 men, all had some degree of arterial insufficiency on Doppler blood flow studies, and 6 had bilateral arterial insufficiency. In addition, 4 of the 10 men also exhibited veno-occlusive abnormalities. Rogers et al. have likewise documented that preservation of accessory pudendal arteries during radical prostatectomy may enhance recovery of sexual function in both its interval and completeness. Preserving accessory pudendal arteries, which may be the principal blood supply to the corpora cavernosa, will result in earlier return of erections and improved postoperative rigidity.

In those patients undergoing radiation therapy, relative radiation dose to the penile bulb appears to be associated with ED. This radiation dose to the penile bulb has also been suggested to be an etiologic explanation for ED in patients undergoing brachytherapy. Radiation injury to the periprostatic tissues can also result in nerve injury. Because radiation effects are of slow onset and long progression, ED may not appear until 1–3 years after completion of treatment.

### Prevalence of erectile dysfunction following prostate cancer treatment

The prevalence of ED in men over 50 is greater than 50%, with more than 10% of such men having complete ED, and this prevalence rises with age such that more than 30% of men over the age of 60 have complete ED. These data must be clearly considered when evaluating the return of erectile function following treatment of prostate cancer. Initial results from nerve-sparing prostatectomy prior to the advent of clinically standardized questionnaires suggested significant improvements in erectile function in men following radical prostatectomy in the younger age group. Indeed men under age 50 had a >90% recovery of erections compared with <25% in those men over 70 years of age. Subsequent studies have confirmed the importance of bilateral nerve-sparing prostatectomy and age. Catalona et al., using standardized questionnaires, showed that 91% of men under 50 with bilateral nerve-sparing prostatectomy experienced return of potency by 24 months postoperatively compared with only 50% with unilateral nerve-sparing prostatectomy. In men in their 50s, return of potency was 82% and 33%, respectively; in men in their 60s, 61% and 51%, respectively in men in their 70s, 48% and 40%, respectively. Scardino et al. reported similar data with further restoration of erectile function between 24 and 36 months. In patients less than 60 years of age who underwent bilateral nerve-sparing prostatectomy, full erection was reported in 70% at 24 months vs 76% at 36 months. This difference between the groups was also demonstrated at all age groups. While also seen in patients with unilateral nerve-sparing prostatectomy, the improvement was less robust in patients less than 60 years of age, improving from only 26% to 30% between 24 and 36 months. Saranchuck et al. showed that improvement in erectile function after radical prostatectomy plateaus at 24–30 months after surgery and that beyond that little additional ED improvement is seen.

While these reports from centers of excellence are encouraging, other studies examining the results of radical prostatectomy in a community-based population do not support this high return of erectile function. Stanford et al., using a medicare database in patients undergoing radical prostatectomy of mixed variety and followed for more than 18 months, found that 60% of patients reported ED. Similarly, Rabbani et al. followed 200 men who were potent preoperatively for 2–51 months and found progressive improvement in erectile function from 12 to 48 months. Of the men studied, 145 were fully potent preoperatively as measured by International Index of Erectile Function (IIEF) scores >26. At 12 months postoperatively, 22% were normally functional, with only 8% reporting a normal IIEF score. At 24 months, 54% were normally functional, with 28% reporting a normal IIEF score. At 48 months, 83% were normally functional, with 51% reporting a normal IIEF score. While these data are helpful, 49% of the patients at 48 months were using sildenafil.

In a comparison of men undergoing radical prostatectomy or external beam radiation therapy for organ-confined carcinoma of the prostate, data from the CapSure Study suggest comparable rates of sexual function during the first 12 months following treatment. During the second year, however, patients treated with external beam radiation therapy showed a significant decline in sexual function compared with a continued improvement in those patients undergoing radical prostatectomy, supporting the concept of delayed effect on nerve function, penile bulb, and ultimately ED in those patients undergoing even the best-designed conformal radiation therapy. Mantz et al., in a study of 114 men with localized prostate cancer undergoing conformal external beam radiation therapy with a mean follow-up of 18.5 months, also demonstrated a declining erectile function rate with time. They reported ED in 2% of pre-radiation potent men at 1 month, 8% at 12 months, 25% at 24 months, and 33% at 36 months.

While the studies investigating erectile function following brachytherapy are few, data suggest that brachytherapy is also associated with delayed-onset ED. Burnett et al. reported a meta-analysis of risk for ED of between 36% and 63% for external beam radiation therapy. Sanchez-Ortiz et al. reported 171 men undergoing brachytherapy for organ-confined carcinoma of the prostate with a mean age of
9 years and followed for 25 months.25 At 2 years following brachytherapy, 51% reported complete or partial ED. The meta-analysis noted previously reports an ED rate of between 14% and 61% with brachytherapy.

Cryotherapy also has few studies with small number of patients followed for evaluation of erectile function. Chaikin et al. reported 36 men assessed using the Global Assessment Question by a telephone questionnaire at 12 months after cryotherapy.26 Of the 28 respondents, 90% reported severe or complete ED.26 Shelley et al. reported 38 patients followed for 36 months following cryotherapy for localized carcinoma of the prostate; 13% of these patients had recovered satisfactory potency while an additional 34% were able to achieve satisfactory erections using sildenafil, injection therapy, intraurethral therapy, or a vacuum erection device.27 Long et al. reported an 84% rate of ED at 1 and 2 years of follow-up,28 while Bahn et al. reported that 47% of patients followed for 3 years have restoration of erectile function.29 Ismael et al. reported a rate of complete ED of 86% for salvage cryotherapy after radiation therapy.30

Thus, it is clear that all methods of treatment of localized carcinoma of the prostate are associated with ED. The accumulating data, both in basic science laboratories and in men followed postoperatively, suggest that nerve damage or long-lasting neuropathy may result in significant corpus cavernosum apoptosis of smooth muscle cells, especially in the sub tunical area associated with endothelial cell dysfunction, and ultimately in destruction: this apoptosis of smooth muscle in the corpus cavernosum leads ultimately to significant veno-occlusive incompetence and ultimately to ED. With the significant prevalence of accessory pudendal arterial supply to the corpora cavernosa, injury to this arterial supply to the penis may also increase apoptosis and decrease oxygen supply and transport to the corpus cavernosum, resulting in veno-occlusive incompetence. This process, purportedly mediated through an increased production of transforming growth factor (TGF)-beta ultimately results in tissue damage, corpus smooth muscle fibrosis, and in some patients decreased penile length.31,32

Postoperative penile rehabilitation

Maintaining erectile function following the treatment of carcinoma of the prostate is theoretically best carried out by preserving arterial inflow and nerve supply to the corpus cavernosum. Despite this concept of maintaining smooth muscle health during resolution of postoperative neuropathy, improving oxygenation of the corpus cavernosum smooth muscle while healing is taking place is likely to improve ultimate outcomes and return of erectile function. While the concept of prophylactic or preventative rehabilitation of ED following treatment of carcinoma of the prostate is enticing, there are few data to clearly support this concept. The first clinical study to suggest that prophylaxis is effective was reported by Montorsi et al. using intracorporeal injection therapy with alprostadil beginning 4 weeks following nerve-sparing radical prostatectomy. The authors divided their postoperative patients into those receiving alprostadil injections three times weekly and those receiving observation only. In the patients receiving injection therapy, 67% reported return of spontaneous erections sufficient for satisfactory coitus compared with only 20% in the observation group.33

In a similar study, Brock et al. evaluated return of spontaneous erections in a group of men using intracavernous alprostadil injection for restoration of erectile function and for coitus.34 These investigators showed an improvement in penile hemodynamics and a return or improvement in spontaneous erections in men with arteriogenic ED.

The introduction of phosphodiesterase (PDE) inhibitors for the effective oral treatment of ED has stimulated interest in the use of these agents for the prophylaxis of ED following nerve-sparing radical prostatectomy. These agents have been demonstrated to stimulate nocturnal erections in men with both normal and deficient erectile function, suggesting that regular use of a PDE-5 inhibitor may improve vascular flow and oxygenation of the corpus cavernosum smooth muscle tissue while the neuropaxia associated with radical prostatectomy resolves. Montorsi et al. demonstrated that sildenafil 100 mg taken at bedtime would lead to a significant increase in nocturnal erections compared with placebo.35 While studies to support the use of PDE-5 inhibitors for prophylaxis are few, Padma-Nathan et al. reported a multicenter placebo controlled prospective study using sildenafil 50 mg or 100 mg at bedtime beginning 4 weeks following nerve-sparing radical prostatectomy. Patients were treated prophylactically for 36 weeks and assessed 8 weeks after discontinuation of treatment. Rigorous outcome measures of erectile function were used, including the IIEF score. At the time of assessment, with patients in both groups taking no sildenafil, 27% of patients who had previously received sildenafil demonstrated return of normal spontaneous erections as measured by an IIEF score of >8 for questions asking whether erections were rigid enough for penetration and satisfactory for completion of sexual intercourse. This compared with 4% in the placebo group (p = 0.0156). A subset of these patients underwent nocturnal penile tumescence (NPT) RigiScan studies, the findings of which supported the questionnaire-based results. Although the return of erectile function in 27% of patients is less than would be expected in populations of patients undergoing adequate nerve-sparing prostatectomy, the difference between treated and placebo patients strongly suggests that maintaining oxygenation with prophylactic treatment during resolution of neuropathy is an important concept in treatment of patients following radical prostatectomy.36 A recent study from our institution reviewed 27 patients undergoing free-hand bilateral nerve-sparing radical laparoscopic prostatectomy. Patients were begun on postoperative day 1 with tadalafil 20 mg, dosed every 3 days. Outcome measurements included presence of erections, success of intercourse, and IIEF questionnaires. At 6 weeks, 16 of 18 patients reported erections, with 9 of 18 having successful intercourse. At 6 months, 9 of 9 patients in this preliminary report had erections, with 7 of 9 having successful intercourse. IIEF scores for both erectile function and intercourse satisfaction improved from 6 weeks to 6 months, the erectile function domain measuring 15.8 at 6 weeks and 17 at 6 months (out of a maximum of 30) and intercourse satisfaction measuring 7.5 at 6 weeks and 8.0 at 6 months (out of a maximum of 15).37
Treatment of erectile dysfunction following prostate cancer treatment

In men with ED following treatment of carcinoma of the prostate, a number of treatment alternatives are currently available. Expectant therapy is reasonable since erectile function improves with time following nerve-sparing radical prostatectomy. Rehabilitation with treatment for ED, however, as has been discussed may improve ultimate outcomes and permit sexual function during the healing process. Initial treatment should be carried out with the most conservative and effective treatment available. This usually represents the use of oral medications, most commonly the PDE-5 inhibitors. Currently there are three PDE-5 inhibitors available throughout most of the world: sildenafil, tadalafil, and vardenafil. Each of these agents has undergone testing in patients following radical prostatectomy. Sildenafil, the first of these agents to be marketed for use in men with ED, has been used in more than 25 million men worldwide with excellent efficacy in restoring erectile function and safety. Contraindications for all PDE-5 inhibitors in patients using nitrate medications for cardiovascular disease are important to note; however, the cardiovascular profile of all three PDE-5 inhibitors confirms the safety of these agents in most aging men with a variety of etiologies for ED.

Sildenafil, the first PDE-5 agent to be used in post radical prostatectomy patients, demonstrated initial results of 43% improvement in erections compared with 15% for placebo. Because this population was mixed, including men who had undergone nerve-sparing prostatectomy and men who had undergone non-nerve-sparing prostatectomy, further stratification of patients was used to demonstrate a 72% improvement in erection in those patients undergoing bilateral nerve-sparing prostatectomy. Subsequent reports by Zippe et al. strongly supported the improvement in response to sildenafil in those patients undergoing bilateral nerve-sparing prostatectomy. While those patients undergoing unilateral nerve sparing were in an intermediate category, those patients without nerve sparing had absent erectile response. A partner study performed by the same group reflected similar outcomes in partners of the patients reported in this study. Hong et al. also demonstrated improvement in erectile function with sildenafil treatment and increasing time from radical prostatectomy. Ability to penetrate, reported by Zippe et al. with sildenafil, was 71.7% with bilateral nerve-sparing surgery, 50% with unilateral nerve-sparing surgery, and 15.4% with non-nerve-sparing surgery (p = 0.001). Spousal satisfaction for these same patients was 66%, 41.6%, and 15.4%, respectively (p = 0.001). Feng et al. studied 316 patients 1–4 years following radical prostatectomy and demonstrated response to sildenafil of 26% at less than 6 months, 36% at 6–12 months, 50% at 12–18 months, and 60% at 18–24 months, again reflecting the improvement in erectile function with time.

In a trial of 303 patients at North American and European centers, patients were treated for 3 months in a double-blind placebo-controlled trial of tadalafil 20 mg versus placebo. Intercourse success rates were measured with the Sexual Event Profile (SEP) as well as the Global Assessment Question (GAQ). In all patients evaluated, 23% of patients responded to placebo compared with 62% to tadalafil on the GAQ. If the patients who had some residual function following surgery were separated, 24% responded to placebo compared with 71% to tadalafil 20 mg (p < 0.001). When using the more rigorous end-point of the SEP question 3 (‘Did your erection last long enough to have successful intercourse?’) 19% of the total group responded to placebo compared with 41% to tadalafil. In those with some residual function, 26% responded positively to placebo compared with 52% to tadalafil. This demonstrates that tadalafil is successful after radical prostatectomy but that patients who had some residual function were more likely to be successful than those patients without residual function following surgery. This method of evaluating data may standardize patients for better surgical procedures and more effective nerve sparing.

Vardenafil has likewise undergone a double-blind, placebo-controlled, multicenter study to evaluate its effectiveness in patients following bilateral nerve-sparing radical prostatectomy. In a global study of 427 men aged 44–77 years, patients were treated in a double-blind placebo-controlled cross-over 12-week study employing vardenafil 10 mg and 20 mg and placebo. In this bilateral and unilateral nerve-sparing prostatectomy group, GAQ was positive in 13% of patients taking placebo compared with 59% of men taking vardenafil 10 mg and 65% of men taking vardenafil 20 mg (p < 0.0001). When using the SEP question 3, 10% responded affirmatively to placebo compared with 37% to vardenafil 10 mg and 34% to vardenafil 20 mg.

In summary, PDE-5 inhibitors appear to be the most convenient and effective method for treatment of ED following radical prostatectomy. The use of PDE-5 prophylaxis, although still controversial, appears to be a safe and effective way of improving the physiology of the corpus cavernosum and of maintaining oxygenation and smooth muscle health while the neuropraxia following radical prostatectomy resolves. In those patients with ED following radical prostatectomy, however, the use of PDE-5 inhibitors appears to be effective for the treatment of ED following nerve-sparing prostatectomy. Successful results are best with excellent nerve-sparing operations and increasing time following radical prostatectomy to permit resolution of neuropraxia. Because head-to-head studies are not available for patients following radical prostatectomy, the relative effectiveness of the various PDE-5 inhibitors in this setting cannot be adequately assessed.

Failure of phosphodiesterase type 5 inhibitor therapy

In patients in whom PDE-5 inhibitor therapy fails, a number of options are available. These include combination therapy, vacuum erection devices, intracavernosal injection therapy, intracavernosal therapy, and penile prosthesis implantation. Each of these methods for treatment was available before the introduction of PDE-5 inhibitors and continues to be useful, effective, and safe for patients with ED following treatment of prostate cancer.
Combination therapy has been used in a variety of forms following radical prostatectomy. The use of combination of intrarectal alprostadil with oral sildenafil has been successfully used in several studies. Nehra et al. reported 28 men failing intrarectal alprostadil or sildenafil.44 Of these 28 men, 17 had undergone radical prostatectomy, 15 of which were bilateral nerve-sparing procedures. All 17 were demonstrated to have veno-occlusive incompetence. Patients were crossed over to the other alternative of therapy and failed this crossover. Once after failure, patients were treated with a combination of intrarectal alprostadil 500μg and placebo. All 28 patients had successful erectile function and intercourse, and continued to use the medication an average of 3.6 times monthly for 30 months. Mydlo et al. likewise combined intracavernosal alprostadil with sildenafil.45 In a group of men who failed each of these therapies, more than 90% were successfully treated with a combination of intrarectal alprostadil and sildenafil. This included 19 patients following radical prostatectomy. Intrarectal alprostadil has been used alone and, as noted above, with sildenafil for the treatment of ED following radical prostatectomy. Costabile et al. reported on 384 patients following radical prostatectomy and ED treated with medicated urethral suppository for erection (MUSE). Responses showed that 70.3% had sufficient erections when MUSE was first administered in the office and that 57.1% had erections satisfactory for normal function at home.46 Raina et al., more recently, reported a series of 54 men treated with intrarectal alprostadil and followed with the Sexual Health Inventory for Men (SHIM). A total of 55% of men achieved and maintained sufficient erectile function for coitus and 48% continued long-term therapy, averaging more than 2 years.47 Compliance with intrarectal alprostadil in this series was 63%. Adverse events of transurethral alprostadil in both series included urethral and penile pain and burning, as well as inadequate erections.

Intracavernosal injection therapy has been used for more than two decades. The use of intrarectal alprostadil injection for prophylaxis was previously discussed.49 Use of intracavernosal alprostadil injection for the treatment of ED in men following radical prostatectomy has been demonstrated to be effective for many years. Linet and Gronic reported satisfactory sexual activity in responders to intracavernosal alprostadil in 94% of injections.50 Principal adverse events included penile pain, and rarely, prolonged erections. Claro et al. also demonstrated significant success rates using a trimix of papaverine, phentolamine, and prostaglandin-E1, with 94.6% of patients having erections satisfactory for vaginal penetration.51 Mydlo et al., in a retrospective study, treated 34 men who had undergone nerve-sparing radical prostatectomy with subsequent ED with a combination of sildenafil or vardenafil plus intracavernosal injection. Of patients who failed oral therapy, 68% responded to intracavernosal injection therapy.52 Unfortunately, patient compliance with intracavernosal injection therapy and maintenance of this method of treatment has been demonstrated to be limited. Because of the invasiveness of therapy, progressive decreases in response, and difficulty with therapy, many patients will discontinue intracavernosal injection with time. Many patients, however, on long-term intracavernous therapy if they are satisfactory responders may respond to a switch to PDE-5 inhibitors. Indeed, Raina et al. evaluated 49 men following radical prostatectomy who had responded to intracavernosal injection therapy but who desired less invasive therapy. Patients were treated with sildenafil 50mg or 100mg and only 19% of patients found sildenafil to be suboptimal. In a group of patients with lower SHIM scores on injection therapy, patients continued to use sildenafil occasionally, enhancing their erections in combination with intracavernosal injection therapy.53 Adverse events associated with intracavernosal injection therapy are well known, and include painful erections, ecchymosis and hematoma of the injection site, and prolonged erections.

Vacuum erection devices (VEDs) have also been widely used for patients following radical prostatectomy. While the VED has been available for many years and was developed by a patient who had a non-nerve-sparing radical prostatectomy, its effectiveness is limited to patients with poor response to pharmacologic therapy. Opsomer et al. treated 110 men with ED with VED. These patients were effectively treated for ED with no significant complications.50 Baniel et al. treated 85 men with postradical prostatectomy ED. Seventy-eight (92%) responded to VED with erections satisfactory for vaginal penetration. Only 11 (14%), however, agreed to continue VED treatment at home. At 1 year, 7 (9%) continued to use VED and another 4 patients (5%) used a combination of VED and intracorporal injection.51 Adverse events associated with VED include corporeal fibrosis, pain, and inhibition of ejaculation.

In patients in whom less invasive therapeutic alternatives fail, implantation of inflatable penile prosthesis is an excellent method for rehabilitation following radical prostatectomy. Penile prostheses have long been used for the treatment of ED of various etiologies with excellent results in patients who are not candidates for, or who respond poorly to, less invasive therapy. With newer penile prostheses, mechanical reliability after 5 years approaches 90%, and at 5–10 years, 91% of patients have erections suitable for coitus. Indeed, patients feel strongly that they would undergo the procedure again and are quite satisfied with treatment.54 In patients with non-nerve-sparing prostatectomies or in those with high risk for ED, penile prostheses can be placed at the time of prostatectomy. Good results have also been reported with placement of the prosthesis reservoir at the time of surgery.54 Indeed, patients who have had previous inflatable penile prostheses can easily, safely, and effectively undergo radical retropubic prostatectomy for carcinoma of the prostate with expected continued device function and low morbidity.55 Simultaneous placement is also possible at the time of radical prostatectomy.56

Similar excellent results have been demonstrated with penile prostheses following external beam radiation therapy for prostate cancer. Duboqc et al. followed 34 patients who had received external beam radiation therapy for organ-confined prostate cancer.57 The average age was 67 years and patients were followed up for a mean 40 months. No patients sustained infection or erosion and 71% of patients used their prosthesis once per week or more for sexual intercourse, 17% used it twice monthly, and 12% were not sexually active although their implant continued to function normally.
Erectile dysfunction and treatment of carcinoma of the prostate

No increase in complications or morbidity was identified in these patients. Carson et al., in a multicenter study, compared patients without radical prostatectomy with those who had undergone radical prostatectomy.\textsuperscript{53} No difference was found between the groups in device infection or mechanical malfunction rates, or in inflation. Indeed, when asked about erections suitable for coitus, 90% of patients with radical prostatectomy responded affirmatively, compared with 90.6% of those patients without radical prostatectomy. In answer to the satisfaction question, ‘Would you undergo the procedure again?’ 90.4% of radical prostatectomy patients responded affirmatively compared with 86.5% of patients without radical prostatectomy.\textsuperscript{53}

Evaluation of nerve function during radical prostatectomy for preservation and nerve replacement has long been pursued. Because identification of the cavernous nerves is difficult and because there is a plexus rather than a defined nerve structure, localization can be challenging. Nerve localization, therefore, has been purported to be helpful in nerve preservation, especially in patients with malignancy close to or through the prostatic capsule. Lue et al. reported the use of an intraoperative nerve-stimulation device associated with monitoring of penile tumescence.\textsuperscript{28} This electrode array device is placed where cavernous nerves are suspected to be and a biphasic current is applied to the nerve bundles. Beginning at low intensities of 8 mA and increasing to 20 mA, the cavernous nerves are stimulated, which results in penile tumescence, which is monitored by a mercury penile strain gauge. Changes in cavernosal tumescence as small as 0.5% can be measured. Because of the multineuronal character of the neurovascular bundle, however, responses are variable and sometimes include detumescence as well as tumescence: if stimulation is predominantly sympathetic and less parasympathetic, detumescence may be expected. Clinical studies by Klotz and Herschorn in 21 men with erections preoperatively and identification of neurovascular bundles using the caverMAP device, only 2 of 19 patients with good intraoperative responses and surgery designed to preserve the areas identified had inadequate erections postoperatively, a response of 94%.\textsuperscript{39} In a subsequent multicenter study, 35 patients were evaluated 12 months following intraoperative pudendal nerve stimulation (caverMAP)-assisted nerve-sparing radical prostatectomy. While 31% of patients had a bilateral caverMAP response and 27 patients had a unilateral caverMAP response (with 3 patients having no response), there was no significant difference among the three groups in erectile function. A multi-institutional study performed in the USA evaluated 50 patients for caverMAP stimulation during radical prostatectomy. All patients had organ-confined carcinoma of the prostate and satisfactory response to preoperative IIEF questions. Patients were less than 60 years old and were followed for 3, 6, and 12 months following surgery. A total of 90% of these patients had successful bilateral nerve-sparing radical prostatectomy, with 10% undergoing unilateral nerve-sparing prostatectomy. A positive response from stimulation was observed in 87.8%, but responses included tumescence and detumescence, detumescence alone, and tumescence. Tumescence alone was found in only 6.4% of patients. Review of the data demonstrated a high sensitivity (88%), but a disappointingly low specificity (54%). The authors – high-volume radical prostatectomy surgeons – felt that the role for intraoperative neurostimulation was limited.\textsuperscript{60} While the use of the caverMAP and nerve stimulation at the time of radical prostatectomy is interesting and potentially useful, the current device and its results suggest the need for a more effective neurostimulation device for the technique to be clinically useful for most urologic surgeons.

Cavernous nerve interposition grafting

Nerve grafting has been used widely by the neurosurgery community for peripheral nerve resection and regeneration using both autologous nerve interposition grafts and nerve conduits. The results of these nerve regeneration procedures vary with surgeon, nerve location, and patient response. Because most of these nerves are specific nerve bundles and not nerve plexuses, the use of cavernous nerve interposition grafts is more challenging. Clearly, however, nerve grafts in patients who are not candidates for bilateral nerve-sparing radical prostatectomy may improve postoperative rehabilitation and erectile function. Kim et al., in 1999, reported a technique for the use of sural nerve interposition grafting in patients who underwent non-nerve-sparing prostatectomy for locally extensive or high-grade carcinoma of the prostate.\textsuperscript{61} The patients who had non-nerve-sparing prostatectomy would be expected to have little or no erectile function both early and in late follow-up. A total of 23 of 28 initially grafted men were followed at least 12 months.\textsuperscript{62} Of the patients followed, 26% had spontaneous erections without PDE-5 inhibitors, 26% had partial erections, and 48% had no response. With the use of sildenafil, however, the ability to achieve satisfactory vaginal penetration was increased to 43%. Using historical controls, only 1 of 70 non-nerve-sparing prostatectomy patients would be expected to respond. Similarly, the data from Zippe et al. with non-nerve-sparing prostatectomy suggest that only 15% of patients will respond to sildenafil.\textsuperscript{60} While this study was not placebo-controlled, neither was it randomized nor blinded, it appears to demonstrate some effectiveness of sural nerve grafting in the restoration of normal erectile function. In an additional study reported by Chang et al. of 30 patients followed for 23 months, 18 (60%) had erectile function with 43% capable of vaginal penetration.\textsuperscript{63} This includes 7 patients (23%) without sildenafil and 6 patients (20%) using sildenafil. In a review of 44 patients undergoing nerve grafting, Secin reported a 34% rate of erectile function but a consistent rate of penetration of only 11%. No correlation for success was found when assessing for patient age, nerve used, hormone therapy, salvage radiation therapy, or ED medications.

While these data are indeed interesting, the number of current patients undergoing non-nerve-sparing radical prostatectomy is limited. It is clear that the nerve-grafting procedure has a significant learning curve and should be confined to centers with significant experience in harvesting and placing the sural nerve graft. Even with expert surgical procedures, however, available studies are not conclusive in reporting the effectiveness of nerve grafting and improving erectile outcomes.\textsuperscript{64}
Compliance

Quality of life studies have consistently reported that erectile and sexual function are important to patients and their partners after prostate cancer treatment, and the age of patients treated for prostate cancer continues to decline. However, several studies have reported poor patient compliance and interest in being treated for erectile and sexual concerns.65 This disconnection between patient concerns, quality of life, and compliance with treatment is indeed concerning and may represent a need for physicians and healthcare providers to encourage patients and partners, to be available for counseling, and to continue to follow sexual dysfunction as closely as the cancer status of these men.

Conclusion

Because prostate cancer occurs in men in the middle and older age groups, risk factors for ED are significant. All prostate cancer treatments increase the risk of ED. While the treatments are associated with organic causes of ED, diagnosis of prostate cancer may be associated with psychogenic causes of ED and sexual dysfunction for both the patient and his partner.

In the 21st century, however, effective treatment alternatives are available for patients with prostate cancer who want to continue to have functional erections. Prophylactic therapy may, in the future, provide an excellent method for maintaining functional penile physiology during the resolution of neuropraxia. Prophylaxis using PDE-5 inhibitors may preserve smooth muscle and endothelial function for future satisfactory erectile function. In those patients needing ED therapy following treatment for prostate cancer, PDE-5 inhibitors continue to be the first-line therapy. In those patients in whom PDE-5 inhibitors fail, combination therapy, intraurethral alprostadil, intracavernosal injection therapy, and VED therapy are all non-surgical alternatives. In those patients in whom less invasive therapy fails or who prefer a more definitive treatment alternative, penile prosthesis implantation will restore erectile function effectively and with excellent postoperative results and satisfaction rates. The development of further techniques for identifying periprostatic nerve bundles and replacing damaged nerves may be helpful. The use of nerve growth factors and neuroregenerative strategies, as well as gene therapy to replace or supplement poorly functioning corpus cavernosum smooth muscle tissue, may provide additional alternatives for the prophylaxis and treatment of these patients in the years to come.

REFERENCES


Vascular risk factors and erectile dysfunction

Graham Jackson and Alethea Cooper

Introduction

With the introduction of the phosphodiesterase (PDE) type 5 inhibitors came a better understanding of the causes of erectile dysfunction (ED). Previously believed to be predominantly a psychological problem, ED is now recognized to be mainly organic in origin. However men with an organic cause may also have psychological problems as a consequence, and men with principally a psychological etiology may also have organic issues. Therefore it is important not to be too rigid when attributing cause and effect and to address all aspects of each patient’s presentation. Whatever the risk factors we need to remember individual patients need help not statistics, though statistics guide management.

Penile erection is a vascular event under neural control and is determined by the balance between arterial inflow and venous outflow. Vascular arterial abnormalities will therefore affect erectile function and it is vasculogenic ED that has been the subject of detailed evaluation. Endothelial dysfunction is now recognized to be the fundamental fault leading to ED. As the endothelium is the same in the penile arteries as the coronary arteries, ED and coronary artery disease (CAD) share the same vascular risk factors (Table 15.1). The greater weight of endothelium relative to the smaller penile arteries might explain why ED can preceed a cardiac event or predict subclinical CAD and in turn why ED is common in the presence of known CAD.

The identification of vascular risk factors has been important not just to our understanding of mechanisms of disease – in this case ED – but has allowed therapeutic targeting of the endothelium with resulting clinical benefit.

Vascular risk factors

Risk factors are associated with but not necessarily causative of vascular disease. They can be considered unavoidable (age, sex, family history) or modifiable (lifestyle, obesity, physical inactivity, cigarette smoking, diabetes, hypertension, and hyperlipidemia). In addition, the metabolic syndrome, which is a cluster of vascular risk factors, including central obesity, hyperlipidemia, hypertension, and insulin resistance is associated with both ED and hypogonadism.

Whilst endothelial dysfunction remains the common denominator linking ED to vascular disease, the role of inflammatory markers reflecting low-grade systemic inflammation has provided further insight into the mechanistic aspects, offering a potential diagnostic role and therapeutic target. This review focuses mainly on modifiable risk factors.

Lifestyle

One of the most important developments has been the role of intensive lifestyle modification in improving erectile function and decreasing cardiovascular inflammatory markers of risk. Atheromatous plaques are complex and dynamic and it is plaque composition rather than volume that influences the risk of a clinical cardiac event. A reduction in lipid content of the plaque and the accumulation of macrophages and lymphocytes, whilst increasing vascular smooth muscle cells (VSMC) and the thickness of the fibrous cap, will improve endothelial function, whereas VSMC apoptosis will reduce cap thickness, increase the necrotic content and plaque inflammation, leading to plaque instability and vulnerability. Most atheroma is sub-clinical and in its early phases more easily influenced in a beneficial way, emphasizing the important link between ED and early phase silent CAD with regard to using ED as a marker for aggressive risk reduction. Indeed, ED may offer the chance to alter the natural history of atherosclerosis throughout the vascular tree and, importantly, the coronary circulation.

The presence of unavoidable risk factors for vascular disease requires the patient to be even more careful regarding reducing modifiable risk factors. We cannot pick our parents or avoid getting older and most men would not wish to change sex, so we should try to make life’s journey as healthy (and enjoyable) as possible. The enjoyable component is fundamental to quality of life – death is a sharp end-point for risk reduction but if length of life is not altered but quality is then risk reduction is just as important.

Obesity and physical activity

It is difficult to separate obesity from physical inactivity and both increase the incidence of ED and CAD. The Rancho Bernado study followed 570 men over 25 years and observed age, overweight [body mass index (BMI) >28kg/m²], and hyperlipidemia were major risk factors for the development of ED and that men with three or more risk factors had a 2.2-fold increased risk of ED compared with men with no baseline risk factors.
In the National Health and Nutrition Examination Survey (NHANES) analysis of data from 2001–2002 involving 3500 men aged over 20 years of age there was an independent association between the risk factors of obesity, smoking, diabetes, and hypertension and the probability of self-reported ED. Obesity conferred a 60% increased ED risk. Longitudinal data from the Massachusetts Male Aging Study (MMAS) showed that a baseline BMI >28 significantly predicted the onset of ED over an 8-year follow-up. In a study from the Netherlands, men aged 50–70 years with a BMI of 25–30 kg/m² increased their odds ratio for ED to 1.5 and those with a BMI >30 kg/m² to 3.0 compared with a normal BMI <25 kg/m².

Therefore obesity has been confirmed as a risk factor for ED in large-scale cross-sectional and longitudinal studies. In the Health Professionals Follow-Up Study (HPFS), the impact of obesity, physical activity, alcohol use, and smoking on ED was assessed in 22,086 men aged 40–75 years over 14 years. Of men who were healthy without overt evidence of cardiovascular disease or diabetes and no ED in 1986, 17.7% developed ED during follow-up. Obesity nearly doubled the risk of ED (multivariate relative risk 1.9 compared with men of ideal weight in 1986). Obesity was found to be a significant independent risk factor for ED in the Men in Australia Telephone Survey (MATeS) study.

Obesity is an independent risk factor for CAD and is associated with elevated levels of inflammatory markers, which are in turn associated with endothelial dysfunction. This low-grade inflammation may be an important pathophysiological link between obesity, ED, and CAD and the metabolic syndrome.

A study of 110 obese men aged 35–55 years with a BMI ≥30 kg/m² (normal ≤25 kg/m²; pre-obese 25–30 kg/m²) assessed the degree to which weight loss combined with increased physical activity affected erectile function. None of the men were diabetic, hypertensive, or hyperlipidemic. In a single-blind fashion, half were randomized to active intervention and half given general information about healthy eating and exercise. The intervention group were given detailed advice about how to lose 10% or more weight, attended monthly group sessions, were set targets, were taught how to reduce calories, and were allocated food diaries. As well as detailed advice about food types they also had personal activity training, including advice on walking, games like soccer, and swimming. After 1 year of monthly meetings with their nutritionalists and exercise trainers they met twice monthly for a further year.

When assessed at 2 years, the BMI had decreased from 36.9 ± 31.2 kg/m² to 36.4 kg/m² in the intervention group and 36.4 kg/m² to 35.7 kg/m² in the control group (p < 0.001). Of interest, the inflammatory markers interleukin 6 (IL-6) also decreased (p = 0.03), as did C-reactive protein (CRP) (p = 0.02). Physical activity increased more in the intervention group, from 48 minutes/week to 195 minutes/week compared with an increase of 51 minutes/week to 84 minutes/week in the controls (p < 0.001). ED improved significantly more in the intervention group, with their International Index of Erectile Function (IIEF) score increasing from a mean of 13.9 to 17 (p < 0.001), and in 17 men the score was over 22 (Figure 15.1). The mean score in the control group was stable (13.5 to 13.6) though 3 men achieved a score over 22. The authors showed, using multivariate analysis, that improvements in BMI and physical activity as well as in CRP, were independently and significantly associated with an improved IIEF score. They concluded that one-third of obese men with ED can improve their erectile function as a result of intensive lifestyle changes. They also identified a reduction in inflammatory markers, which may well have had a significant impact on endothelial function, emphasizing again the link between obesity, ED, and CAD.

The potential clinical cardiovascular benefit is worth emphasizing. ED often precedes a cardiac event by 2–3 years, and cardiac events are associated with increased levels of circulating inflammatory and endothelial-prothrombotic markers. By reducing the risk factors for ED we may, within the 2–3 year time window, reduce or prevent a subsequent cardiovascular event.

A sedentary, inactive life has been linked to ED (Figure 15.2). In the HPFS, ED was associated with the level of physical

### Table 15.1 Shared risk factors between coronary artery disease and erectile dysfunction

<table>
<thead>
<tr>
<th>Coronary artery disease</th>
<th>Erectile dysfunction</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
<td>Age</td>
</tr>
<tr>
<td>Dyslipidemia</td>
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<tr>
<td>Obesity</td>
<td>Obesity</td>
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<tr>
<td>Depression</td>
<td>Depression</td>
</tr>
<tr>
<td>Male sex</td>
<td>Coronary artery disease, peripheral vascular disease</td>
</tr>
</tbody>
</table>

![Figure 15.1](image-url) Individual changes in erectile function score of obese men. Data markers with error bars indicate mean (SD). IIEF, International Index of Erectile Function. From JAMA 2004; 291: 2978–84.
activity as well as BMI. When the men were categorized according to their level of physical fitness, the less active (those with higher levels of sedentary behavior) were independently linked to ED. All types of exercise reduced the incidence of ED. Running at least 2.5 hours a week was associated with a 30% relative risk reduction for ED compared with no regular activity, and 1.5 hours running or 3 hours of rigorous outdoor work reduced the relative risk by 20%.

In the Global Study of Sexual Attitudes and Behaviour (GSSAB), 31.8% of men who had less than average levels of physical activity had ED compared with 13.9% of men who exercised more than average. Lack of exercise therefore increased the ED risk 2.5 times.

In the MMAS, 593 men without ED at baseline and with no evidence of heart disease, diabetes, or prostate cancer were followed for 8 years. Men who were initially sedentary but took up exercise had a lower risk of ED compared with those who remained inactive throughout.

The cardiovascular benefit of regular exercise is well known, as is the increased risk from both obesity and inactivity. Regular physical activity (20–30 minutes or more each day) to the point of slight breathlessness (‘can walk and talk’) is beneficial with regard to reducing the likelihood of a cardiac event or recurrence after an event. At 12 years in the HPFS of 44,452 men aged 40–75 years brisk walking for 30 minutes a day reduced the incidence of CAD by 18%. In the British Regional Heart Study (BRHS), which examined changes in physical activity over 14 years in 5934 men aged 40–59 years at baseline, men who took up even light activity experienced a 34% mortality reduction over the subsequent 4 years even though the exercise was taken up in later life. Similar exercise-related benefits have been recorded for stroke. Because ED and CAD increase in incidence with age and because weight loss and increased physical activity reduce the development of both, the recommendation ‘physically fit = sexually fit’ unites the mechanistic with the clinical end-point reality.

With obesity increasing the incidence of ED by 30%, and weight loss combined with physical activity decreasing ED by 30%, the Princeton Consensus emphasized the importance of lifestyle intervention, particularly in men with ED and CAD, because of the benefit throughout the vascular tree.

**Smoking**

In HPFS, smoking increased the risk of developing ED by 50%. In MMAS, men who smoked at baseline increased their risk of developing moderate or total ED to 24% compared to non-smokers, at 14% (p = 0.01). In hypertensive men the probability of complete ED was doubled. Smoking has been shown to interfere significantly and adversely with the cavernous veno-occlusive mechanism and to reduce erectile response to intracavernous injections.

Cigarette smoking is arguably the leading preventable cause of CAD. The risk compared with that of non-smokers is increased by 60%. Peripheral vascular disease occurs in only 6% of middle-aged adults who do not smoke, in 12% of ex-smokers, and in 18% of current smokers. Following smoking cessation the CAD risk falls within months and reaches the level of non-smokers in 3–5 years.

The benefit of smoking cessation on ED is not proven, perhaps owing to an irreversible effect from prolonged tobacco use. Chronic smoking leads to a considerable decrease in penile and neuronal nitric oxide synthase (NOS) activity. Neuronal NOS may be subject to increased degradation, or damage to nerve terminals (i.e. a tobacco-related neuropathy) may be responsible for the lack of a perceived benefit from smoking cessation, since penile endothelial NOS appears to react to electrical field stimulation.

When considering overall vascular health, advice and support to enable patients to stop smoking is an essential lifestyle intervention.
The metabolic syndrome

The metabolic syndrome consists of a cluster of risk factors that increase the risk of cardiovascular disease and type 2 diabetes. It is characterized by abdominal obesity, hyperlipidemia, glucose intolerance, hypertension, and insulin resistance. It is associated with pro-inflammatory markers and endothelial dysfunction and an increased incidence of moderate to severe ED in men over 50 years of age. Furthermore, ED may predict the metabolic syndrome in men with a BMI < 25 kg/m² who otherwise would be considered to be at low cardiovascular risk.

As the components of the metabolic syndrome increase so does the presence of organic ED. In addition there has been reported a three-fold increase in the prevalence of hypogonadism, and as the number of criteria for the metabolic syndrome increases so does the incidence of hypogonadism. The strong association between the metabolic syndrome and hypogonadism has led to the speculation that testosterone replacement might be a therapeutic option. To date, however, the evidence primarily supports a lifestyle approach.

The Mediterranean-style diet (rich in whole grain, fruits, vegetables, legumes, and walnut and olive oil) was evaluated in 35 men with 30 acting as controls. All had the metabolic syndrome and ED. The intervention group were given detailed dietary advice, targets were set, and monthly small-group sessions offered for support. Men in the control group were given general oral and written information about healthy foods but no individualized support. After 2 years markers of endothelial function and inflammation significantly improved in the intervention group but not the control group. In the intervention group, 13 men achieved an IIEF of 22 or higher compared with only 2 in the control group. The intervention group had a significant decrease in glucose, insulin, low-density lipoprotein (LDL) cholesterol, triglycerides, and blood pressure with a significant increase in high-density lipoprotein (HDL) cholesterol. Fourteen men in the intervention group had glucose intolerance and 6 had diabetes at baseline, but by 2 years the number had reduced to 8 and 3, respectively.

The metabolic syndrome was evaluated in the West of Scotland Coronary Prevention Study (WOSCOPS), which studied 6000 men over 5 years. The metabolic syndrome was associated with a 3.7-fold increased risk for CAD and a 24.5-fold increased risk for the development of diabetes.

Several studies have shown that lifestyle modification is the first-line treatment for the metabolic syndrome, with focused pharmacological treatment controlling hyperlipidemia, hypertension, and hyperglycemia conferring additional benefit where indicated.

What we see here is the evidence of multiple risk factor reduction benefiting a multiple risk factor state in terms of both ED and CAD risk. There is also emerging a potentially important link between inflammatory markers and their modification in the ED/CAD context and its therapy.

Alcohol

Excess alcohol intake per se increases cardiovascular risk but there is little evidence of an ED risk other than the acute effect of binge drinking. In addition men with a very high alcohol intake are unlikely to participate in studies of risk association and reduction so data are at present inconclusive.

Specific cardiovascular risk factors

Hypertension, hyperlipidemia, and diabetes increase the risk of ED and CAD. ED in the absence of cardiac symptoms predicts a subsequent cardiac event in a significant number of men. The lifestyle changes already discussed will have a beneficial impact on these risk factors.

Hyperlipidemia inhibits NOS. A high level of LDL cholesterol and a low level of HDL cholesterol increase the risk of developing ED, probably because of impaired endothelium-dependent relaxation. Many clinical trials evaluating lipid-lowering therapy, mainly with statins, have demonstrated increased plaque stability and reduced cardiac and cerebral events to be more effective than dietary advice. Unfortunately, lipid-lowering therapy with statins and fibrates can cause reversible ED. Statins are more likely to induce ED in men with multiple cardiovascular risk factors. A small study reported improved ED in men treated with atorvastatin and sildenafil compared with sildenafil alone, which fits with the observation that the effectiveness of sildenafil is increased in the presence of good metabolic cardiovascular risk factor control.

Hypertension is a major risk factor for both ED and CAD. Cavernous artery insufficiency was reported in 85% of 117 hypertensive patients. ED is present in up to 17% of men at the initial hypertensive diagnosis. The incidence rate of ED in treated hypertensives is 68% (7.6% mild, 15.4% moderate, and 45.2% severe according to the IIEF). It is believed that underlying vascular disease (i.e. the impact of hypertension on the endothelium) is the main cause of hypertensive ED, though drug therapies may exacerbate the problem. Treatment hypertension is associated with ED, especially if thiazide drugs are used.Valsartan, an angiotensin II receptor antagonist, has been shown to not induce ED compared with the combined beta- and alpha-blocker carvedilol. This may be as a result of angiotensin II upregulating PDE-5 and its antagonism neutralizing this effect. The importance of asking about ED before initiating therapy and mentioning the potential adverse effect of therapy is an essential part of treatment, facilitating patient adherence to therapy. If ED is a problem when managing hypertension, using valsartan and the alpha-blocker doxazosin minimizes the risk of ED developing as an adverse effect.

Diabetes is recognized to be a 'cardiovascular equivalent' so that a man with diabetes and no cardiac history is considered to have the same cardiac risk as a non-diabetic who has already sustained a myocardial infarct. ED is a common complication of diabetes affecting over 50% of diabetic men. The cause is a combination of autonomic neuropathy, peripheral vascular disease, CAD, drug therapy, and at times psychological factors. In the MMAS, complete ED occurred three times more frequently in diabetics than non-diabetics. ED is more common than diabetic retinopathy or nephropathy and may be the first sign of diabetes in 12% of patients. In a study of 133 men with type 2 diabetes and angiographically confirmed silent CAD compared with 127 men with diabetes and no evidence of myocardial ischemia (non-invasively evaluated), the
prevalence of ED in those with silent CAD was 34% and those without 4.7% \((p = 0.0001)\). ED was an independent predictor of silent CAD above hyperlipidemia, smoking, and microalbuminuria. Therefore a diabetic with ED and no cardiac history is at significantly higher risk of CAD than a diabetic without ED.

**Depression**

Depressive disorders range from mild symptoms to major depression with core symptoms of sadness or loss interest or pleasure in usual activities for a period of at least 2 weeks accompanied by at least five of the following: sleep difficulties, fatigue, low self-esteem, guilt, psychomotor agitation or retardation, and loss of appetite. Not surprisingly depressive symptoms may cause loss of libido and reduced sexual function but, conversely, ED may also lead to depression. Cross-sectional studies have demonstrated a relationship between ED and depression but it remains unclear whether depression causes ED and, if so, what the underlying mechanism may be. The evidence that depression promotes CAD events in clinically healthy people as well as in patients with known coronary heart disease is more established.\(^4\) By analogy, it is conceivable that depression may cause vascular disease in the penile arteries, therefore providing another link to ED. Analysis of cross-sectional results from the MMAS a decade ago established a relationship between ED and depression independent of aging, level of education, heart disease, diabetes, physical activity, and other potential confounders.\(^47\)

Symptoms of depression (measured using the Centre for Epidemiologic Depression Scale (CES-D) and defined as a score ≥16) were present in 12% of men with both ED and depression across all ages. The estimated odds ratio for ED was 1.82 in men who had depressive symptoms compared with those who did not.

In the MMAS, men were followed up for an average of 8.8 years, enabling a prospective analysis of a possible causative relationship between depression and ED.\(^48\) Excluding men with ED, diabetes, or heart disease at baseline (as well as those who had undergone radical prostatectomy), 778 men were studied. Symptoms of depression were present in 9% at baseline. At follow-up 168 of the men were classified as having moderate or complete ED (by self-administered questionnaire with specific items as well as by a single-item global self-assessment). However, the presence of depressive symptoms at baseline was not a significant predictor of incident ED \((p = 0.12)\), with a greater percentage of men without depressive symptoms developing ED than those with depressive symptoms at baseline (21.3% vs 13.2%).

This result is at odds with the conclusion of a study of 1683 men aged 50, 60, or 70 years from a Finnish cohort, 11.4% of whom demonstrated depressive symptoms (a score of ≥16 on the five-item version of the Mental Health Index) at baseline in a 5-year follow-up study.\(^49\) In men free of ED at baseline (determined by two self-report items, adapted from the questionnaire used in the MMAS), the incidence of ED at 5 years was 59 per 1000 person-years (95% CI 39–90) in men with depressive mood and 37 per 1000 person-years (95% CI 32–43) in men without depressive symptoms. After controlling for possible confounding variables (age, education, marital status, BMI, smoking, diabetes, hypertension, heart disease, cerebrovascular disease, and medication use), the incidence of ED was 4.5 times higher in men with treated depressive symptoms at follow-up, but just 1.2 times higher in those with untreated depressive symptoms at follow-up, compared with those free of depressive symptoms and not taking medication for psychological disorders at baseline. In men free of depressive symptoms but who used antipsychotic medication, the risk of ED was doubled. The adjusted incidence density ratio of depressive mood was 1.9 (95% CI 1.1–3.3) in men with ED compared with those without it at baseline. The authors describe a bi-directional relationship between depression and ED, stating that ED may independently cause or increase depression, and that moderate or severe depressive mood or antidepressant medication may cause ED. A suggested mechanism is decreased blood flow to the penis and inhibition of penile smooth muscle relaxation resulting from depression inhibiting the activity of parasympathetic nerves. The authors suggest low power in the MMAS as an explanation for the discrepancy between the MMAS results and their study.

The results of the Finnish study highlight the potential for antidepressant medication to cause ED. Drugs such as tricyclic antidepressants and selective serotonin reuptake inhibitors, which are commonly used to treat depression, may be associated with male sexual dysfunction, including new-onset ED, and they should be taken into consideration when treating depression.\(^50\)

Further evidence is needed to support a bi-directional relationship, but given the well-supported association between ED and depression, it is appropriate that patients presenting with ED should be screened for depression and vice versa.

**Conclusion**

ED and CAD frequently co-exist, and ED may occur 2–3 years before a cardiac event. ED and CAD share the same vascular risk factors and a man with ED with or without CAD history should have his risk factors aggressively treated. Low-grade inflammation links ED and CAD and is increased with increasing lifestyle risk factors and decreased with intervention. ED is predominantly a vascular disease and, like diabetes, it should be considered a ‘cardiovascular equivalent’.

**REFERENCES**

16 Mediterranean diet and erectile dysfunction

Dario Giugliano, Myriam Ciotola, Francesco Giugliano, Massimo D’Armiento, and Katherine Esposito

Introduction

Erectile dysfunction (ED) is one of the most common chronic disorders, affecting more than 100 million men worldwide; 30 million men in the United States may have ED. Sexual problems appear to be widespread in society, influenced by both health-related and psychosocial factors, and they are associated with impaired quality of life. Although many treatment options are available, none of them offers a complete response in all patients. Thus, as with many other medical diseases, prevention may be the most effective approach to alleviating the consequences of sexual dysfunctions.

Lifestyle and erectile dysfunction

Epidemiological studies suggest that modifiable health behaviors are associated with a reduced risk of ED. In the Health Professionals Follow-up Study, several modifiable lifestyle factors, including physical activity and leanness, were associated with maintenance of good erectile function. For instance, men with a body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters) higher than 28.7 are likely to carry a 30% higher risk of erectile dysfunction than those with a normal BMI (25 or lower). Similarly, men in the highest quintile of physical activity carry a 30% lower risk of ED than those in the referent quintile (sedentary men). The link between physical activity and ED seems to be operative also in diabetic men. Information on erectile function was obtained in 1040 diabetic patients selected from male patients (age >18 years) treated in 26 diabetes clinics in Israel: leisure time and work-related physical activity and consumption of small amounts of alcohol were found to be protective: 0.51 (odds ratio 0.36–0.72) and 0.70 (0.51–0.97), respectively. Data from other surveys also indicate a higher prevalence of impotence in obese, sedentary men. Prospective studies, such as the 9-year follow-up study from the Massachusetts Male Aging Study (MMAS) and the 25-year follow-up Rancho Bernardo Study, reported that body weight was an independent risk factor for ED, with a risk exceeding 90% of controls (odds ratios 1.93 and 1.96, respectively). In general, subjects with ED tend to be heavier with a greater waist measurement than subjects without ED, and they are also more likely to be hypertensive and hypercholesterolemic.

Although the relationship between obesity and ED may not be readily apparent, a growing body of evidence implicates central adiposity as key regulator of inflammation. Among the various adipokines released by the visceral adipocytes, both tumor necrosis factor-alpha and interleukin (IL)-6 seem to play a major role since they can depress endothelial function. As endothelial dysfunction is increasingly acknowledged as an early sign of generalized atherosclerosis and associates with ED, one possible mechanism linking obesity to ED may be through the increased release of adipokines.

We evaluated associations between erectile function, endothelial function and markers of systemic vascular inflammation in 80 obese men, aged 35–55 years, divided into two equal groups according to the presence or absence of erectile dysfunction. Compared with non-obese age-matched men, obese men had impaired indices of endothelial function and higher circulating concentrations of the proinflammatory cytokines IL-6, IL-8, and IL-18, as well as C-reactive protein (CRP). Endothelial function showed a greater impairment in impotent obese men as compared with potent obese men, while circulating CRP levels were significantly higher in obese men with erectile dysfunction (Table 16.1). The association between International Index of Erectile Function (IIEF) score and indices of endothelial dysfunction supports the presence of a possible common vascular pathway underlying both conditions in obese men. Defective nitric oxide (NO) activity, linked to reduced NO availability, could provide a unifying explanation for this association (Figure 16.1). In particular, in isolated corpus cavernosum strips from patients with erectile dysfunction, both neurogenic and endothelium-dependent relaxation are impaired.

Strong epidemiological evidence links the subsequent risk of erectile dysfunction to the presence of well-recognized risk factors for coronary heart disease, such as smoking, diabetes, hypertension, and dyslipidemia. Interestingly enough, all these factors are linked to lifestyle. As four of the five components of the metabolic syndrome are risk factors for erectile dysfunction and are also characterized by abnormal endothelial function, we postulated an association between erectile dysfunction and the metabolic syndrome, and tested the hypothesis that erectile dysfunction was more prevalent in men with the metabolic syndrome. Compared with 50 age- and weight-matched control subjects, 100 patients with the metabolic syndrome had an increased prevalence of erectile dysfunction (26.7% vs 13%, \( p=0.03 \)); moreover, there was an
increase in erectile dysfunction prevalence (IIEF <21) as the number of components of the metabolic syndrome increased, associated with a linear increase in CRP levels and a linear impairment of endothelial function score, suggesting that the cumulative burden of cardiovascular risk may be central to the pathogenesis of ED (Figure 16.2).

Dietary factors and erectile dysfunction

A high prevalence of ED in patients with cardiovascular risk factors has been reported.6,17 Moreover, patients with ED have an increased prevalence of coronary heart disease (CHD) and peripheral vascular diseases.18 Kaiser et al. have shown that subjects with ED but without evidence of clinical cardiovascular disease and free of traditional cardiovascular risk factors present widespread abnormality of endothelial function,19 as has been seen in patients with cardiovascular risk factors. According to a rising popular view, subjects with ED seem to have a vascular mechanism similar to that seen in atherosclerosis11 and therefore a diagnosis of ED may be seen as a sentinel event that should prompt investigation for CHD in asymptomatic men.20

As ED and atherosclerosis may share some pathways,21 it seems reasonable to assume that dietary factors, which are so important in reducing the burden of CHD disease,22 may also play a role in reducing the occurrence of ED. For example, there are several observational studies associating the Mediterranean diet with a lower risk of CHD morbidity and mortality.23-26 Moreover, some randomized clinical trials have shown a beneficial effect of this dietary pattern on secondary prevention of CHD.27,28 The effect of the Mediterranean diet on CHD can be mediated through multiple biological pathways other than serum lipids, including reduction of oxidative stress and subclinical inflammation, amelioration of endothelial dysfunction and insulin sensitivity, and mitigation of blood pressure and thrombotic tendency.29,30

We have found that the intake of some foods was less represented in subjects with ED;4 in particular, the calculated intakes of vegetables, fruits, and nuts, and the ratio of monounsaturated to saturated lipids were significantly lower in men with ED (Figures 16.3 and 16.4). Interestingly, each of these nutrients has been associated with a decreased risk of CHD, through an effect of improving endothelial dysfunction31 and decreasing inflammation.32 In general, the intake of foods that are more likely to be associated with an increased CHD risk was higher in men with ED, whereas the intake of foods that are associated with a decreased CHD risk was reduced.

The concept of dietary patterns has recently attracted considerable interest in the field of nutritional epidemiology.33

| Table 16.1 Correlations between International Index of Erectile Function (IIEF) score and metabolic parameters, cytokine levels, and indices of endothelial function in 80 obese men with erectile dysfunction. |
|---|---|---|
| IIEF score | p Value |
| Weight | −0.40 | <0.01 |
| BMI | −0.37 | <0.01 |
| WHR | −0.35 | <0.01 |
| Glucose | −0.08 | =0.15 |
| Insulin | −0.04 | =0.24 |
| Cholesterol | −0.15 | =0.08 |
| HDL-Cholesterol | 0.08 | =0.09 |
| Triglycerides | −0.09 | =0.12 |
| IL-6* | −0.10 | =0.06 |
| IL-8* | −0.18 | <0.05 |
| IL-18* | −0.14 | =0.08 |
| CRP* | −0.25 | <0.02 |

Log-transformed data. BMI, body mass index; WHR, waist–hip ratio; HDL, high-density lipoprotein; IL, interleukin; CRP, C-reactive protein.

Adapted from J Endocrinol Invest 2004; 27: 665–9.13

Figure 16.1 Lifestyle choices may cause early injury in endothelial cells through oxidative stress, with resultant decreased availability of nitric oxide (NO).

Figure 16.2 In 100 patients with the metabolic syndrome, the prevalence of erectile dysfunction (ED) (bottom) increases with the number of components of the syndrome, in association with an increase in C-reactive protein (CRP) levels and a reduction in endothelial function score (middle). Adapted from Diabetes Care 2005; 28: 1201–3.16
In a sub-cohort of healthy men from the Health Professionals Follow-up Study, Fung et al. discerned two major dietary patterns: the prudent pattern, characterized by higher intake of fruit, vegetables, whole grains, and poultry; and the Western pattern, characterized by a higher intake of red meat, high-fat dairy products, and refined grains. A positive correlation has been found between the Western dietary pattern and plasma biomarkers of obesity and cardiovascular disease risk, such as plasma concentrations of markers of inflammatory dysfunction (CRP) and endothelial dysfunction [intercellular adhesion molecule (ICAM)-1, vascular cell adhesion molecule (VCAM)-1, and P-selectin]. Moreover, a dietary pattern that was high in sugar-sweetened soft drinks, refined grains, diet soft drinks, and processed meat but low in wine, coffee, cruciferous vegetables, and yellow vegetables was associated with an increased risk of diabetes and inflammatory markers in the Nurses’ Healthy Study. As inflammation may play a causative role in ED, a reduced low-grade inflammation brought about by healthy dietary patterns may be implicated in the association of increasing adherence to Mediterranean diet and reduced prevalence of ED.

In our study, we found that a dietary pattern that was high in fruit, vegetables, nuts, whole grains, and fish but low in red and processed meat and refined grains was more represented in men without ED than in men with ED. This dietary pattern is quite similar to the traditional Mediterranean diet, which is characterized by a high intake of vegetables, legumes, fruits and nuts, and cereals, and a high intake of olive oil associated with a low intake of saturated fats, a moderate intake of fish, a low-to-moderate intake of dairy products, a low intake of meat and poultry, and a regular but moderate intake of ethanol, primarily in the form of wine and generally during meals.

The Mediterranean diet

Mortality statistics from the World Health Organization database covering the period 1960 to 1990 have provided
intriguing evidence that something unusual has been affecting, in a beneficial way, the health of the Mediterranean populations, and in particular, with respect to CHD. Even though health care for many of these populations was inferior to that available in northern Europe and North America and the prevalence of smoking was unusually high, death rates in the Mediterranean region were generally lower and adult life expectancy generally higher in comparison with the economically more developed countries, particularly among men.39

In a recent large prospective survey involving about 22,000 adults from Greece (the Greek cohort of the EPIC study), there has been shown to be an inverse correlation between a greater adherence to the Mediterranean diet and death.21 In particular, approximately a two-point increment (out of nine) in the Mediterranean diet score was associated with a 25% reduction in total mortality and a 33% reduction in CHD mortality. These associations were independent of sex, smoking status, level of education, BMI, and level of physical activity. Moreover, the relation was significant among participants 55 years of age or older, but not among younger participants, indicating an increasing cumulative exposure to a healthier diet may be beneficial. In other studies, adherence to similar healthful lifestyle practices has been found to be associated with an 83% reduction in the rate of CHD, a 91% reduction in diabetes in women, and a 71% reduction in colon cancer in men.40 More recently, Knoops et al. from the Netherlands, France, Spain, and Italy, showed that in European men and women aged 70–90 years, adherence to a Mediterranean diet pattern, moderate alcohol consumption, non-smoking status, and physical activity were each associated with a lower rate of all-cause mortality.23 Taken together, the combination was associated with a mortality rate of about one-third that of those with none or only one of these protective factors. These healthy behaviors were not extreme: for example, the physical activity criterion could be met by half an hour of walking daily.

**Interventional studies**

The traditional Mediterranean diet, based on food patterns typical of many regions in Greece and southern Italy in the early 1960s, may be thought as having the components indicated in Table 16.2. The main characteristics of the Mediterranean diet include an abundance of plant food (fruits, vegetables, whole-grain cereals, nuts, and legumes), olive oil as the principal source of fat, fish and poultry consumed in low-to-moderate amounts, a relatively low consumption of red meat, and moderate consumption of wine (normally with meals). So, the dietary patterns that prevail in the Mediterranean region have many common characteristics: total lipid intake may be high, as in Greece (around or in excess of 40% of total energy intake), or moderate, as in Italy (around 30% of total energy intake); the Italian variant of the Mediterranean diet is characterized by a higher consumption of pasta, whereas in Spain, fish consumption is particularly high. In all instances, however, the ratio of monounsaturated to saturated fats is much higher than in other places of the world, including northern Europe and North America. It has become customary to represent the Mediterranean diet in the form of a pyramid, the base of which refers to foods that are to be consumed most frequently and the top to those to be consumed rarely, with the remaining foods occupying intermediate positions.

The first clinical trial evidence in support of the health benefits of the Mediterranean diet came from the Lyon Diet Heart Study,27 in which 605 patients who had had a myocardial infarction were randomly assigned to a Mediterranean-style diet or a control diet resembling the American Heart Association Step I diet. The Lyon Heart Study was aimed to test whether a Mediterranean type of diet may be superior to the classic dietary counseling given by cardiologists in secondary prevention of coronary disease. The Mediterranean diet model supplied 30% of energy from fats and less than 10% of energy from saturated fatty acids. Regarding essential fatty acids, the intake of 18:2(n-6) linoleic acid was restricted to 4% of energy and the intake of 18:3(n-3) alpha-linolenic acid provided more than 0.6% of energy. In practical terms, the dietary instructions could be summarized as follows: more grains and bread; more cereals, legumes and beans; more fresh vegetables and fruits; more fish, less meat (beef, lamb, pork), sausages and luncheon meats (to be replaced by poultry); and no butter and cream (to be replaced by canola oil-based margarine with a trans-fatty acid content of less than 5%). Finally, the oils recommended for salad and cooking were exclusively olive and canola (erucic acid-free rapeseed oil) oils. In the study, the most frequent non-fatal events were new acute myocardial infarction and episodes of unstable angina, which are commonly due to the rupture of an atherosclerotic plaque. The risk of these two end-points was reduced by about 70% by the Mediterranean diet, indicating that the biological changes associated with it resulted in a significant local anti-inflammatory effect. The number of new episodes of heart failure was also reduced in the Mediterranean group. Total cholesterol, systolic blood pressure, leucocyte count, female sex, and aspirin were each significantly and independently associated with recurrence, indicating that the Mediterranean diet does not alter the usual relationships between risk factors of coronary disease and recurrence, at least quantitatively.

Singh et al. tested an ‘Indo-Mediterranean’ diet in 1000 patients in India with existing coronary disease or at high risk of coronary disease.28 Compared with the control diet, the intervention diet—characterized by increased intake of mustard or soybean oil, nuts, vegetables, fruits, and whole grains—reduced

**Table 16.2** Dietary pattern characteristic of the traditional Mediterranean diet

<table>
<thead>
<tr>
<th>Characteristic</th>
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<tr>
<td>High consumption of fruits (3–4 servings/day)</td>
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<tr>
<td>High consumption of vegetables (2–3 servings/day)</td>
</tr>
<tr>
<td>High monounsaturated-to-saturated fat ratio (≥2)</td>
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<tr>
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<td>Low consumption of meat and meat products (4–5 servings/month)</td>
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Mediterranean diet and erectile dysfunction 129
the rate of fatal myocardial infarction by one-third and the rate of sudden death from cardiac causes by two-thirds.

Esposito et al. explored possible mechanisms underlying a dietary intervention. The authors randomized 180 patients (99 men, 81 women) with metabolic syndrome to a Mediterranean-style diet (instructions about increasing daily consumption of whole grains, vegetables, fruits, nuts, and olive oil; n = 90) vs a cardiac-prudent diet with fat intake less than 30% (n = 90). Physical activity increased equally in both groups. After 2 years, body weight decreased more in the intervention group than in the control group, but even after controlling for weight loss, inflammatory markers and insulin resistance declined more in the intervention group than in the control group, whereas endothelial function improved more in the intervention group. Only 40 patients in the intervention group still had metabolic syndrome after 2 years compared with 78 patients on the control diet (Figure 16.5). These results suggest a plausible mechanism for the beneficial effects of the Mediterranean diet.

**Mediterranean diet and erectile dysfunction**

ED and endothelial dysfunction may have some shared pathways, through a defect in NO activity that may be inhibited through age-, disease-, and behavior-related pathways. Intervention on modifiable health behaviors, especially reducing body weight and increasing physical activity, may in theory be a safe strategy to reduce the risk of both ED and endothelial dysfunction. We hypothesized that lifestyle changes aimed at reducing body weight and increasing physical activity would induce amelioration of erectile and endothelial functions in obese men. We conducted a randomized controlled trial involving 110 obese men with ED. Men assigned to the intervention group were entered in an intensive weight-loss program, involving personalized dietary counseling, exercise advice, and regular meetings with a nutritionist and personal trainer. The dietary advice was tailored to each man on the basis of food records collected on three non-consecutive days, which had to be done the week before the meeting with the nutritionist. Men in the control group were given general oral and written information about healthy food choices and exercise at baseline and at subsequent bimonthly visits, but no specific individualized programs were offered to them. After 2 years, men randomized to the intervention had lost significantly more weight, had increased their physical activity, had experienced favorable changes in physiologic measures of endothelial dysfunction, and had significant improvement in their ED score compared with men in the control group (Figure 16.6).

This study provided evidence that sustained lifestyle changes can partially ameliorate ED in obese men. In the Massachusetts Male Aging Study, Derby et al. found that men who were overweight at baseline were at an increased risk of developing erectile dysfunction regardless of whether they lost weight during the follow-up records. About one-third of obese men with ED regained their sexual activity after 2 years of adopting healthy behaviors, mainly regular exercise, a Mediterranean-style diet, and weight reduction. This may be in line with epidemiological evidence that physical activity was associated with a 30% lower risk of ED, while obesity was associated with a 30% higher risk of ED. Additionally, men in the intervention program showed improvement in the number of surrogate traditional and novel cardiovascular risk factors, which were better than those seen in control men.

We analyzed the effect of Mediterranean diet on ED in subjects with the metabolic syndrome. Sixty-five men with the metabolic syndrome and ED were enrolled in the study; 35 out of them were assigned to the intervention diet and 30 to
the control diet (Figure 16.7). The recommended composition of the dietary regimen was carbohydrates 50–60%, proteins 15–20%, total fat <30%, saturated fat <10%, and <300 mg of cholesterol consumed per day. Moreover, subjects were advised to consume at least 250–300 g of fruits, 125–150 g of vegetables, and 25–50 g of nuts per day; in addition, they were also encouraged to consume 400 g of whole grains (legumes, rice, maize, and wheat) daily and to increase the consumption of olive oil.

After 2 years, men on the Mediterranean diet consumed a greater percentage of calories from polyunsaturated and mono-unsaturated fat, and they had a greater intake of omega-3 fatty acids and a lower intake of saturated fat than controls. Total fruit, vegetable, nuts, and whole grain intakes and olive oil consumption were also significantly higher in the intervention group. There were 13 men in the intervention group and 2 in the control group (p = 0.015) that reported an IIEF score of 22 or higher. In the intervention group, changes in IIEF score were related to increased intake of fruits, vegetables, nuts, and legumes (p < 0.01) and to the ratio of polyunsaturated to saturated lipids (p < 0.02). Nutrient intake (34% of the variance, p = 0.01), endothelial function score (14% of the variance, p = 0.045), and CRP (16% of the variance, p = 0.03) were independent predictors of IIEF score and explained almost 64% of the variability in its changes.

Conclusion

Men with ED show, compared with age-matched men without ED, a difference in lifestyle attitudes that may play a role in the development and progression of ED. In particular, the prevalence of unhealthy dietary patterns and physical inactivity were significantly higher in men with ED. At a time in which obesity and the metabolic syndrome have become a public health crisis, modification of behavioral risk factors is strongly suggested to halt the progression of the epidemic and may also be a safe strategy for dealing with the ongoing increase in sexual problems in the population.

Despite increased public awareness of the importance of diet in decreasing the risk of chronic disease, large gaps remain in food-based recommendations and actual dietary practice of the population. A substantial body of knowledge demonstrates that the abundant consumption of food of plant origin, including vegetables, fruit, and whole grains, convey a markedly lower risk of coronary disease. From a public health perspective it is not essential to wait for elucidation of every mechanism underlying health promotion activities and interventions; given the simplicity of the diet quality score, increasing the intake of recommended foods represents a practical recommendation for improving health. A recent statement from the American Heart Association declares that the most prudent and scientifically supportable recommendation for the general population is to consume a balanced diet with an emphasis on antioxidant-rich fruits and vegetables and on whole grains. When diet provides a sufficient supply of antioxidants, there is no need for supplements.

Higher levels of consumption of olive oil are considered to be the hallmark of the traditional Mediterranean diet. Other important plant-based sources of monounsaturated fatty acids include nuts and canola (rapeseed) oil. Monounsaturated fat, whether from olive oil or other sources, may have the same beneficial effects on blood lipids and oxidative stress, but this possibility has not been fully studied. Both the Lyon Diet Heart Study and the recent Indian study have emphasized canola (rapeseed) oil as a source of alpha-linolenic acid. Thus, a Mediterranean-type diet, with high intake of fruits, vegetables, nuts, legumes, and minimally processed grains, despite differences resulting from its ‘translation’ into other cultures, can use food options beyond olive oil for increasing the intake of monounsaturated fats and polyunsaturated fats at the expense of saturated and trans-fats and refined carbohydrates.

Figure 16.7 Effect of a Mediterranean-style diet on the International Index of Erectile Function (IIEF) score in patients with metabolic syndrome and erectile dysfunction at baseline. In the intervention group (Mediterranean diet), patients experienced a significant improvement in IIEF score. Adapted from Int J Impot Res 2006; 18: 405–10.43
Dietary patterns in Greece and other Mediterranean countries are changing rapidly, with increased consumption of saturated fat and refined carbohydrates. The healthy Mediterranean diet in Italy is being abandoned by the population. From a historic perspective the association of the Mediterranean diet with some of the greatest ancient civilizations – Greek, Etruscan, and Roman – may have been coincidental, although the pioneering British nutritionist John Waterlow has argued: ‘It is difficult to conceive how the Greeks and Romans could have achieved such remarkable feats, which involved far more than a small elite, if they had not in general had an adequate and nourishing diet’.

Dietary factors may be important in the development of ED, and for claims for the widespread application of current nutritional guidelines, which insist upon increasing consumption of vegetables, fruit, nuts and healthy fats, the intake of which is less represented in ED patients. There is enough scientific evidence to indicate that consumption of unhealthy diets may be a causative factor in progression of atherogenesis (Figure 16.8). Promotion of healthful lifestyles (including Mediterranean-style diets and exercise) for primary prevention, among people of all ages, may yield great benefits and reduce the burden of chronic diseases, including the burden of sexual dysfunction.

REFERENCES


Figure 16.8 In the postprandial state, acute variations in plasma glucose and lipid levels following ingestion of unhealthy foods may cause endothelial dysfunction, which is considered one important factor in the development of erectile dysfunction (ED). FFA, free fatty acids; NO, nitric oxide; ET-1, endothelin-1; AT, Angiotensin II; oxLDL, oxidized LDL lipoprotein.


Pharmacological risk factors for altered male sexual function

Michael G Wyllie

Introduction

Until recently, iatrogenic sexual dysfunction was rarely listed with drug precautions; such effects were considered to be unfortunate, but predictable. Although these effects were viewed as relatively unimportant compared with the primary therapeutic benefits, actual or anticipated male sexual dysfunction caused patient non-compliance with drug therapies and reluctance to undergo surgical procedures. These events produced significant changes in pharmaceutical marketing, research, and clinical practice. First, the limited profitability of drug therapies that produced sexual disorders led to an appreciation of quality-of-life issues. This, in turn, led to the development of new drug therapies with fewer side-effects. The identification of sexual side-effects of drugs in humans, coupled with concomitant characterization in animals, provided a foundation for pharmacological strategies to treat sexual disorders. Judicious exploitation of side-effects is being employed to treat different types of sexual complaints, such as premature ejaculation. This overview provides examples of iatrogenic sexual dysfunction associated with drug treatments.

Erectile dysfunction due to prescription medications is under-reported but paradoxically a wide range of drugs have been implicated with altered sexual function (Table 17.1).

There are several classification schemes for grouping drugs with sexual side-effects. The most common has been categorization by therapeutic indication, for example anti-hypertensives, antidepressants and antiandrogens. However, therapeutic indications do not necessarily describe the mechanism or site of action of the iatrogenic effects, with the exception of androgen blockers. An alternative scheme is to segregate drugs by their mechanisms of action on the sexual response cascade: interest, performance, satisfaction. Since this classification is the same as that used for designing new drugs to alleviate sexual disorders, it provides a link between preclinical studies that explore the origins of male sexual function and clinical studies that exploit novel or existing pharmacological preparations for the treatment of sexual interest, performance and satisfaction. The subdivisions of this classification scheme include: a central behavioral component, a central–spinal reflex component, and an end-organ component. Drugs are also segregated by effect, as being psychopharmacological, neuropharmacological, and smooth muscle or vascular drugs.

Drug-induced effects on the behavioral component on sexual response

The behavioral component of sexual response encompasses the integration of sensory inputs with the cognitive, emotional, and desire components for the initiation and maintenance of sexual drive. These agents are often separated into psychopharmacological drugs and neuropharmacological drugs; however, the distinction between psychopharmacological and neuropharmacological is ambiguous, because specific neural pathways of human male sexual function have not been completely identified and psychotropic effects could influence any aspect of the neural integration. The most obvious effects noted by the patient and the clinician are those on general behavior or specific sexual behavior. Drugs with general sedative effects that can alter sexual behavior include antihypertensives, anticonvulsants, hypnotics, anorexics, antidepressants, antipsychotics, and anxiolytics.

Direct effects on sexual behavior occur through effects on the brain areas responsible for regulating sexual drive. These areas include the medial pre-optic area (MPOA) of the ventral diencephalon, the mesencephalic central gray nucleus, the amygdala, and the hippocampus. These areas, particularly the MPOA, are thought to be responsible for sexual drive and emotional control of peripheral sexual reflexes. Pharmacological and histochemical studies have identified a variety of receptor subtypes in the MPOA, including peptidergic, cholinergic, dopaminergic, adrenergic and serotoninergic receptors, and receptors for reproductive hormones. The monoaminergic and hormonal receptors have been the most extensively studied.

Sexual dimorphism of the central nervous system (CNS) is regulated by fetal and neonatal levels of circulating androgens and estrogens: sexual behavior can be altered by changes in the MPOA induced by supplementation or denial of sex steroids. Yet, in adults, there is a poor correlation between circulating testosterone levels and measures of sexual interest, sexual activity, or erectile function. Among geriatric patients, the complaint of impotence and the incidence of hypogonadism are statistically independent. Not surprisingly, endocrinopathy as the cause of impotence is variable, with an incidence from 1 to 35%. Despite routine endocrine
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**Anticholinergics**

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**Antipsychotics**

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**Anxiolytics**

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<td>Cyproterone acetate</td>
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screening in the evaluation of male sexual dysfunction, the exact role of androgen levels in erectile dysfunction (ED) remains to be elucidated. With castration, sexual function may range from a complete loss of libido to continued normal sexual activity. Spontaneous nocturnal erections are androgen-dependent. Erections in response to visual erotic stimuli, on the other hand, appear to be independent of androgens.

Another consequence of pharmacological or surgical castration is hot flushes, which occur in the majority of patients (77% and 58%, respectively). The physiology is poorly understood, but is believed to be related to changes in the hypothalamus which is in proximity to the thermoregulatory system.

Dopaminergic mechanisms
One of the milestone observations on the psychopharmacological control of sexual response was the finding of increased libido in parkinsonian, psychiatric, and impotent patients receiving the catecholamine precursor L-dopa. In laboratory animals and patient populations, similar effects were also observed with deprenyl (a monoamine oxidase B inhibitor), cocaine (a catecholamine reuptake inhibitor), and amphetamine (a catecholamine-releasing agent). In contrast to these stimulatory effects, suppression of sexual behavior in animals and of libido in patients has been reported with reserpine and alpha-methyl-dopa, which deplete functional pools of catecholamines in neurons. These results suggest the involvement of dopaminergic or adrenergic receptors (or both) in the central regulation of sexual drive.

The theory of dopaminergic receptor involvement is further supported by the observations of increased libido in patients treated with dopamine agonists (apomorphine and pergolide) and dopamine reuptake inhibitors (nomifensine and bupropion). In animal studies, activation of central dopaminergic receptors by systemic administration of the agonists apomorphine or quinolol increases sexual behavior in rats at doses that do not affect prolactin secretion or elicit other responses. In contrast to dopaminergic agonists, dopaminergic antagonists (antipsychotics) suppress sexual drive in both patients and animals. In addition to the effects on central and peripheral neuronal function, dopaminergic antagonists can also suppress sexual responses through the induction of hyperprolactinemia and secondary hypogonadism. Currently, bromocriptine is the only dopaminergic agonist approved for treating erectile disorders, but only for hyperprolactinemia-induced dysfunction.

Adrenergic mechanisms
Adrenergic receptors have important roles in the central control of sexual response. Amplification of noradrenergic transmission with a selective norepinephrine reuptake inhibitor, viloxazine, markedly increased libido in depressed patients. These effects did not correlate with the antidepressant activity of this compound. There have been a few clinical reports

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<tr>
<th>Drug type</th>
<th>Libido or desire</th>
<th>Erectile function</th>
<th>Ejaculatory function</th>
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<td>Verapamil</td>
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Table 17.1 Continued
of decreased libido with alpha-1-adrenergic antagonists (prazosin and phenoxbenzamine), alpha-2-adrenergic agonists (clonidine), and beta-adrenergic antagonists (propranolol). The reports match animal investigations in males, with either prazosin or clonidine suppressing mating behavior and yohimbine, an alpha-2-adrenergic antagonist, increasing sexual behavior.\textsuperscript{22} The psychopharmacological effects of yohimbine may, in part, be responsible for its reported efficacy in the treatment of subgroups of patients with erectile dysfunction.\textsuperscript{21} The stimulatory effect of yohimbine has recently been used to counteract the sexual disorders induced by serotonin reuptake inhibitors (SSRIs, see below).

**Serotonergic mechanisms**

With the recent success of SSRIs and other newly developed serotonergic drugs, knowledge both of the sexual side-effects and of new uses of these agents has rapidly expanded. In preclinical studies, suppression of sexual behavior and subsequently suppression of erectile and ejaculatory response has been demonstrated, with direct or indirect augmentation of central serotonin activity with 5-HT (5-hydroxytryptamine, serotonin) loading, specific serotonin reuptake inhibitors (SSRIs), releasing agents or postsynaptic agonists.\textsuperscript{13,24} These effects correlated with reports of suppressed libido and anorgasmsia in patients treated with the 5-HT-releasing agent fenfluramine and various other SSRIs. The effects of SSRIs in prolonging the latency of the ejaculatory reflex in animals and men has been sufficiently reproduced to be proposed as a therapy for premature ejaculation.

Serotonin may have both facilitating and inhibiting effects on sexual behavior, depending on the receptor subtype, location of receptors and species examined. 5-HT-1A agonists can inhibit erection and promote ejaculation; 5-HT-1C agonists promote erection; 5-HT-2 agonists both inhibit and facilitate various aspects of sexual behavior. 5-HT-1A autoreceptor agonists, such as buspirone, increase sexual behavior in male rats and rhesus monkeys.\textsuperscript{25,26} These studies correlate with the clinical findings on buspirone. In one human trial, buspirone increased libido and other sexual responses in men and female patients with generalized anxiety disorders.\textsuperscript{27} Several more selective and more potent 5-HT-1A agonists have been reported to have robust effects on sexual performance and may become clinical candidates.\textsuperscript{28} In addition to 5-HT-1A autoreceptor agonists, postsynaptic 5-HT-2 receptor antagonists augment sexual behavior and indirectly enhance peripheral sexual reflexes.\textsuperscript{12,24,28} These laboratory studies suggest that 5-HT-2 receptor antagonists can contribute to the enhanced libido and erectile response noted in clinical studies with trazodone.\textsuperscript{29}

**Drug-induced effects on erectile reflexes**

In addition to their effects on the dienccephalic areas involved in sexual regulation, drugs can also suppress or induce the erectile reflex through actions on sites in the brainstem and spinal cord that regulate the autonomic control of erection. These drug-induced disorders of the erectile reflex include failure to initiate erection, failure to maintain erection, spontaneous erections unaccompanied by interest, and priapism.

**Dopaminergic mechanisms**

Dopaminergic agents also affect erectile responses in men and laboratory animals without changing sexual behavior, presumably by altering reflex pathways. Spontaneous erections were first noted as side-effects in patients treated with l-dopa or dopaminergic agonists. Recently, subcutaneously administered apomorphine has been shown to induce penile erections in normal volunteers and patients. Apomorphine induces yawning, stereotypical sexual behavior, and erections in rodents. Erections have been induced in 67\% of psychogenically impotent patients in one series; dosage-related nausea and vomiting have been a problem with both subcutaneous and oral formulations. Presumably, patients must have an intact end-organ (i.e., non-vasculogenic erectile dysfunction) to respond to apomorphine.\textsuperscript{29,30} The response to dopaminergic receptor stimulation with apomorphine is not accompanied by increases in libido.\textsuperscript{30} Although erections have been noted as side-effects of oral dopaminergic agonist therapy, the incidence of this response appears to be far greater with subcutaneous administration. In parallel to these clinical studies, dopaminergic agonist-induced erections have also been observed in rats and rhesus monkeys.\textsuperscript{26} In contrast to agonists, erectile dysfunction is a reported side-effect of drugs with dopaminergic antagonist activity.\textsuperscript{4,8}

**Serotonergic mechanisms**

Unlike dopamine, serotonin appears to have different effects on the central and peripheral components of the sexual response. Amplification of serotonergic activity through the administration of serotonin-releasing agents or agonists also induces spontaneous erections in rats and rhesus monkeys.\textsuperscript{31,32} In contrast, in humans SSRIs result in sexual effects that are primarily suppressive, although case reports of improvements in erectile function have been published.\textsuperscript{33,34} The erectogenic effects of serotonin have been proposed to be mediated by the 5-HT-C receptor subtype.\textsuperscript{6,31} These effects may contribute to the induction of priapism in patients treated with the antidepressant trazodone and to the increase in erectile activity during rapid eye movement (REM) sleep. The primary trazodone metabolite meta-chlorophenyl piperazine (mCPP) is a serotonergic agonist that induces erections in rats and rhesus monkeys and selectively increases the firing rate of the penile nerve and cavernosal blood pressure in rats.\textsuperscript{31,32} These studies indicate that a serotonergic agonist could be useful for erectile dysfunction, particularly if drugs with appropriate receptor specificity can be developed. Again, it must be emphasized that serotonin has both facilitating and inhibiting effects on sexual behavior, depending on the receptor subtype, the location of receptors, and the species being tested.

Major roles for opioid receptors have been proposed, based on a variety of laboratory and clinical studies.\textsuperscript{9,35} The loss of the ability to achieve or maintain erection has been a noted side-effect in heroin- and methadone-addicted patients.\textsuperscript{6,4,9} Decreased sexual desire was also noted in many of these
patients, suggesting a CNS-depressant effect. Spontaneous erections are reported side-effects during treatment with the opiate antagonists naloxone and naltrexone in heroin- or methadone-addicted patients. In a single-blind study with impotent patients, naltrexone produced significant increases compared with placebo in both sexual performance and the number of morning and spontaneous erections; improved sexual performance was reported in 11 of 15 patients with psychogenic impotence. In an uncontrolled study, 6 of 7 idiopathic impotent patients were restored to full erectile function with naltrexone therapy. Naloxone has also been reported to induce full erections lasting an hour in normal volunteers when combined with yohimbine, presumably through the additive effects of these agents on sexual response.

Until recently, iatrogenic erectile dysfunction associated with anticholinergic drugs was thought to be mediated exclusively through a vascular pharmacological mechanism by which anticholinergic drugs block the effects of parasympathetic-induced release of endothelial cell-derived relaxation factors (e.g. nitric oxide, NO) that relax the cavernosal smooth muscle. Regardless of the mechanism, blockade of muscarinic receptors appears to be responsible for the reported erectile failures associated with drugs such as imipramine and other tricyclic antidepressants. The best evidence for this was the discovery that bethanechol could reverse erectile failure caused by these drugs.

Drug therapies that alter sympathetic neural activity also are associated with erectile disorders. The maintenance of the penis in a flaccid condition is dependent upon a continuous stimulation of alpha-1-adrenergic receptors on the smooth muscle of the corpora cavernosa through the tonic release of norepinephrine from sympathetic terminals. It has been proposed that the sinusoidal endothelium also contributes to the maintenance of tone (flaccidity) by synthesis and release of endothelins. Drug regimens that increase peripheral adrenergic tone have been reported to cause erectile failure, whereas those that decrease postsynaptic alpha-1-adrenergic receptor activity are associated with reports of priapism. Chronic treatments with amphetamine and cocaine, which indirectly increase alpha-1-adrenergic receptor activity, have been associated with the side-effect of erectile failure. In contrast, a variety of drugs with alpha-1-adrenergic antagonist activity, as is the case with some antihypertensives and antipsychotics, have been reported to cause priapism. The priapism associated with trazodone has also been theorized to be mediated through its alpha-1-adrenergic antagonist activity. This mechanism may explain the sporadic observation of priapism with drugs possessing alpha-1-adrenergic antagonist activity. These effects also justify the current evaluations of oral alpha-1-adrenergic antagonists for erectile disorders.

Pharmacological studies in vitro on corporal smooth muscle have provided evidence that many new vascular therapies have erekctogenic effects. Since the inadvertent discovery that hypogastric arterial infusion of papaverine induces erection, these agents have been clinically exploited in pharmacological erection programs. The erectile reflex has been modulated at the level of the end-organ by intracavernous injection, and by topical or urethral agents. The most efficacious corporal relaxants act by increasing corporal smooth muscle levels of cAMP (e.g. prostaglandin E1), cGMP (e.g., NO releasers), or cAMP and cGMP (papaverine and other phosphodiesterase inhibitors). The underlying pathophysiology and the drugs developed on this basis are described in other chapters within this textbook.

Drug-induced effects on ejaculatory reflex control

The ejaculatory-phase events include the induction of seminal emission, ejaculation, and perceptual changes associated with orgasm. Agents that alter the ejaculatory phase may do so directly by affecting performance, or indirectly by affecting sexual satisfaction. The predominant drug-induced disorders of this phase include delayed or absent ejaculation, retrograde ejaculation, and suppressed seminal emission. These side-effects are associated with agents that alter the central or peripheral components of the seminal emission–ejaculation reflex. As in the case of the behavioral and erectile phases, drugs that affect dopaminergic or serotonergic receptor activity are thought to modulate the central component of the ejaculatory reflex.

In laboratory animals, pharmacological agents that increase dopaminergic receptor activity shorten ejaculatory latency and induce seminal emission in normal animals and restore ejaculatory capacity to dysfunctional animals. Examples of such agents include l-dopa, deprenyl, and dopaminergic agonists. Conversely, agents that decrease dopaminergic activity (dopamine antagonists) increase ejaculatory latency and reduce ejaculatory capacity. The clinical correlates include premature seminal emission or ejaculation in parkinsonian patients treated with l-dopa or pergolide, and delayed or absent ejaculation in patients treated with antipsychotics. A practical application of this last-named side-effect has been the use of low-dose therapies of thioridazine or metoclopramide to treat premature ejaculation.

The effects of serotonergic agents on ejaculatory reflexes in laboratory animals have been more controversial. In experiments with mating animals, pharmacological agents that increase release or inhibit synaptic uptake of 5-HT or directly stimulate postsynaptic 5-HT receptors have been shown to delay or suppress ejaculatory responses. Agents that decrease serotonergic activity, such as serotonergic neurotoxins or antagonists, have the opposite effect. However, serotonergic agonists and releasing agents can also induce spontaneous ejaculation in animals. In clinical studies with SSRIs, protracted ejaculatory latencies in patients were so reproducible that these agents were employed as treatments for premature ejaculation (see Chapter 62). Other antidepressants that inhibit 5-HT uptake (e.g. tricyclic antidepressants) also produce these side-effects. These clinical effects appear to correlate to the effects observed in animals during mating conditions. Furthermore, anorgasmia induced by tricyclic antidepressants and monoamine oxidase inhibitors (which suppress metabolism of 5-HT) can be reversed by the administration of a serotonergic antagonist, cyproheptadine.

As seminal emission and antegrade ejaculation are processes that are primarily controlled by sympathetic activity,
pharmacological agents that deplete pools of catecholamines or have alpha-1-adrenergic antagonist activity are known to suppress ejaculatory capacity and induce retrograde ejaculation.5,7,8 The agents that diminish preasympotptic norepinephrine release include reserpine, alpha-methyl-Dopa, guanethidine, guanadrel, betahistine, and derisoquine. Other drugs associated with this side-effect have significant alpha-1-adrenergic antagonist activity; these include the antihypertensives phenoxycbenzamine, phen tolamine, prazosin and tamsulosin; and the antipsychotics thioridazine, chlorpromazine, trifluromazine and mesoridazine. In contrast to the effects of alpha-1-adrenergic antagonists, sympathomimetic agents, such as pseudoephedrine, ephedrine, and phenylpropanolamine, have been used to treat retrograde ejaculation.35

REFERENCES

Male sexual dysfunction and the prostate

Michael G Wyllie

Introduction

There is a variety of ways in which the topic of male sexual dysfunction and the prostate could be tackled. However, the content of this chapter is largely restricted to analyzing the impact of drugs used for the treatment of lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH) on sexual function, and the potential utility of phosphodiesterase (PDE) 5 inhibitors in the treatment of LUTS. Covered elsewhere in this textbook is the impact of the urological surgeon. What is not covered is the role of the prostate in normal sexual function. What follows are some key messages rather than a comprehensive review of the literature. The focus is on the information that is most relevant to the management of BPH patients with and without comorbid sexual dysfunction (SD).

The link between benign prostatic hyperplasia, lower urinary tract symptoms, and sexual function

LUTS and sexual dysfunction are highly prevalent in aging men, and both conditions have a significant negative impact on overall quality of life. It would appear that neither BPH nor LUTS per se, when corrected for age, adversely affects sexual function. However, a particularly relevant question is whether or not men with LUTS and BPH are at increased risk of sexual problems. To address this, we must firstly determine what we mean by sexual function. It is more than just erectile function; indeed sexual function should be regarded as encompassing several different aspects or ‘domains.’ Some of these aspects are characterized or captured in the International Index of Erectile Function (IIEF). By way of generalization, male sexual dysfunction may manifest as decreased libido, ejaculatory dysfunction, erectile dysfunction (ED), or a combination of all three of these conditions. As is described below, many of the currently available therapies for LUTS and BPH have the potential to affect sexual function, both negatively and positively, and either acutely or after long-term administration.

Despite evidence based on a large and increasing number of epidemiological studies, such as the Multinational Survey of the Aging Male (MSAM-7) (see below), a causal association between LUTS and ED has not yet been firmly established, although there is a close association. In instances where a relationship has been suggested, the relevance of such reports should be considered in relation to the weight of formal evidence. Warranting particular scrutiny is the strength of the association (as measured by increases in the relative risk of ED with LUTS), the presence of a quantifiable dose–response effect (i.e. does more severe LUTS equate with more severe ED?), and a temporal relationship between the development of these disorders (i.e. disease progression). Most importantly, the observed epidemiological data should be underpinned by having some potential underlying pathophysiological or biological explanation. It is worth pointing out that in this context there is emerging evidence that ED and LUTS have some physiological, pathological, and molecular components in common. In particular, the possibility that they may both result in compromised intra-organ vascular perfusion deserves further investigation.

Several epidemiological studies, either by original design or retrospective subset analysis (caveat emptor) have attempted to examine the relationship between sex and the prostate. One of the more important studies is the MSAM-7, which suggested a strong association between the frequency of sexual intercourse and the patient’s International Prostate Symptom Score (IPSS). The IIEF score was also significantly associated with LUTS severity. Authors have noted that the association between LUTS and sexual dysfunction persisted after controlling for age and other co-morbidities such as hypertension and diabetes, which are known to have an impact on sexual function. Measures of ejaculatory disorders, including reduced ejaculate and ejaculation pain, were also strongly associated with LUTS. The results of the MSAM-7 suggest that the majority of older men have active sex lives and that the severity of LUTS is an independent risk factor for sexual disorders.

Obviously, any therapy that has a negative impact on sexual function would be of considerable concern to the majority of men, but especially to those already experiencing sexual dysfunction or in a high-risk category for the development of sexual dysfunction.

New data are, however, increasingly emerging to indicate potential links at epidemiological, physiological, pathophysiological, and treatment levels between sexual dysfunction and LUTS. If there is some degree of intimate association between BPH and LUTS and sexual dysfunction that is more than coincidental, this may have implications for the clinical management of these disorders, as well as for the development.
of treatment algorithms. For example, treatment of one condition might have an impact, either positive or negative, on the other. In addition, there are specific drug interaction issues, e.g. the potential vasoactive synergy of alpha-blockers and PDE-5 inhibitors that may have to be carefully considered in the treatment algorithm not only for BPH patients but also for patients with ED and comorbid BPH.

However, even assuming there is some degree of comorbidity or shared pathophysiology, the question remains as to why urologists or primary care physicians should worry about sexual dysfunction in men with LUTS. The relationship between the two dysfunctions is important for several reasons:

- Additional information on risk factors for either condition could be important for diagnosis of likely comorbid conditions.
- There is an increasing number of affected men, given the ‘graying’ of the population.
- Many BPH patients have comorbid ED or ejaculatory disorders and do not want an exacerbation or precipitation of their sexual dysfunction.
- Many currently available LUTS treatments (medical and surgical) affect sexual function. The impact of drugs used in the treatment of BPH is summarized immediately below; that of the surgeons is covered elsewhere (see Chapter 64).

### Drugs for benign prostatic hyperplasia and their relationship with sexual dysfunction

Symptomatic BPH (i.e. LUTS) is almost invariably treated with one of two classes of agents – either alpha-adrenoceptor antagonists (alpha-blockers) or members of the ‘prostate-shrinking’ 5-alpha-reductase inhibitor class. In general, despite reasonably convincing data and dozens of abstracts on the clinical advantages of combination therapy, each drug class is generally used as monotherapy; the clinical benefit perceived by many key academic opinion leaders is perhaps outweighed by cost concerns on the part of patients or their healthcare providers, who are not easily influenced by statistics. The impact of these drugs on sexual function is summarized in qualitative terms in Table 18.1, adapted from a meta-analysis carried out by the AUA and published in 2003.4

### Impact of 5-alpha-reductase inhibitors on sexual function

The first drug class to be widely approved, exemplified by finasteride and dutasteride, was the 5-alpha-reductase inhibitors, commonly referred to as ‘prostate shrinkers’. These drugs act by inhibiting the conversion of testosterone to its primary metabolite, dihydrotestosterone (DHT), which is considered to have the major androgenic influence on the prostatic nuclear androgen receptor. As prostatic proliferation is highly androgen-dependent, the reduction in overall androgenic load thereby reduces prostatic growth and causes regression of the hyperplasia. Evidence showing reduction in prostatic mass or volume has accrued from many long-term studies involving both of the 5-alpha-reductase inhibitors. The onset of clinical benefit (occurring after 6 months’ treatment) is much slower than the almost immediate reduction in intra-prostatic DHT levels, consistent with symptom improvement being secondary to reduction in tissue proliferation or even increased apoptosis. The first 5-alpha-reductase inhibitor, finasteride, inhibits only one isozyme (5-alpha-reductase-2), and dutasteride, an inhibitor of both isozymes, was subsequently developed to overcome perceived efficacy limitations. The assumption behind the development of dutasteride was that a dual isozyme inhibitor would lead to a greater and more rapid reduction in intra-prostatic DHT levels, with corresponding improved efficacy. Evidence has emerged that the reduction in DHT can be more rapid with dutasteride but there is little convincing evidence of efficacy beyond that attained with finasteride.

From the experience – albeit in prostate cancer patients – of more effective androgen ablators (e.g. gonadotropin releasing hormone (GnRH) agonists, which reduce both testosterone and DHT to near castration levels), and from our knowledge of the role of androgens in the control of sexual function, it was predicted by many that the 5-alpha-reductase inhibitors would produce some degree of sexual dysfunction. Although this is the case, at least with respect to reduction in libido and desire, the incidence emerging over almost two decades of 5-alpha-reductase inhibitor therapy, was relatively low (≤5%) and ironically may be lower for dutasteride, the inhibitor of both isozymes, than for finasteride, although direct side-to-side evaluations have not been undertaken. When observed, sexual dysfunction is apparent at time points in clinical trials well before treatment efficacy is observed, consistent with the

| Table 18.1 AUA meta-analysis of outcomes of medical therapies: estimates of occurrence of sexual adverse events. |
| --- | --- | --- | --- |
| Therapy | Ejaculation | Erection | Libido |
| **alpha-blockers** | | | |
| Alfuzosin | – | 3 (1–6) | 1 (0–4) |
| Doxazosin | 0 (0–2) | 4 (1–8) | 3 (2–6) |
| Tamsulosin | 10 (6–15) | 4 (1–8) | – |
| Terazosin | 1 (1–2) | 5 (3–8) | 3 (1–5) |
| **Hormonal** | | | |
| Finasteride | 4 (3–5) | 8 (6–11) | 5 (4–7) |
| **Combined** | | | |
| Alfuzosin/finasteride | 1 (0–2) | 8 (5–11) | 2 (1–4) |
| Doxazosin/finasteride | 3 (2–6) | 10 (7–14) | 3 (1–5) |
| Terazosin/finasteride | 7 (5–10) | 9 (1–13) | 5 (3–8) |
| Placebo | 1 (1–11) | 4 (3–5) | 3 (3–4) |

Adapted from reference 6.
sexual dysfunction being dependent on alteration in androgen load, but temporally related to DHT reduction.

The precise relationship between androgens and any or all aspects of sexual function remains to be established. Testosterone replacement or supplementation has been shown to augment sexual function and restore potency in hypogonadal and ‘normal’ men. Likewise, in support of a link, androgen ablation in prostate cancer patients, as described above, can reduce sexual function. However, there are several anomalies. First, GnRH analogs, such as cetrorelix, although rapidly producing near-castration androgen levels in BPH patients, appear to be largely without effect on sexual function at doses that appear, at least in clinical trials, to improve LUTS dramatically. At least two clinical trials in BPH have shown that cetrorelix is clinically effective within weeks (an anomalously quick onset of action if the effect is secondary to androgen reduction), whereas there is little or no short- or long-term impact on sexual function.8 Secondly, the degree of sexual function observed with chronic administration of 5-alpha-reductase inhibitors is surprisingly low, although DHT levels can be reduced by over 95%.

Impact of alpha-blockers on sexual function

There are even more anomalies in the sexual clinical profile of the alpha-blockers. Alpha-blockers have provided the mainstay of front-line treatment of LUTS for over 25 years, and their clinical profile from billions of patient days is well documented. As a class they were originally assumed to improve symptoms by acting initially on the sympathetic nervous system outflow to periurethral intra-prostatic stromal tissue to reduce urethral resistance and thereby increase uroflow. Secondary to this reduction in obstruction after a few months, an improvement in bladder-based irritative symptoms would be expected. Certainly, the immediate improvement in uroflow (after the first dose) and the time to full effect (12 weeks or so) is consistent with this hypothesis. More recently, evidence has emerged that all symptom improvements can be related to changes in local vascular perfusion within the bladder.9 The alpha-1-adrenoceptor is subdivided into three subtypes, alpha-1A receptors, alpha-1B receptors and alpha-1D receptors. Blockade of the A and D subtypes is generally considered important for the relief of LUTS.

On the basis of our knowledge of the autonomic control of penile erection, alpha-blockers, by reducing the flaccidity-inducing sympathetic nervous system, would be expected to be pro-erectile (Figure 18.1). One has to look closely in the literature to find unequivocal evidence to support this hypothesis. Indeed, alpha-blockers injected intracorporeally at extremely low doses are certainly erectogenic.10 In addition, in reasonably controlled clinical studies, oral doxazosin has been shown to reduce the incidence of ED, and in long-term studies to reduce the appearance of ED11 and to sensitize the corporal tissue to other erectogenic agents.12 The assumption is that this effect represents an extension of the generalized action of the drug on resistance vessels within the penile vasculature rather than any particular specificity of the drug for penile tissue.

It is pertinent to note, and relevant to later discussion on the impact of PDE-5 inhibitors on LUTS symptoms (see below), that Georg Bartsch’s group in Innsbruck has consistently suggested that all effects of alpha-blockers within the urogenital sinus are in fact secondary to changes in local blood flow within target organs – specifically in the case of alpha-blockers in LUTS, changes within the bladder rather than the prostate.9 Consistent with this basic hypothesis, there appears to be a particularly good correlation between alpha-blocker-induced changes in detrusor blood flow and oxygination and improvement in IPSS.

If the LUTS improvement is secondary to local organ vascular perfusion changes, it would be expected that dihydropyridine calcium-channel blockers would be effective, particularly in the many BPH patients with comorbid hypertension. Should this be the case, the incidence of BPH should be less in the many antianginal and antihypertensive clinical trials conducted with calcium-channel blockers than in the equivalent placebo groups and the equivalent age-matched population at large. One for the epidemiologists?

Does the erectogenic action of doxazosin represent a class effect? As with the overall clinical profile of doxazosin, there is some evidence in several studies that alfuzosin improves erectile function whereas neither of the other quinazoline alpha-blockers, prazosin and terazosin, appears to have any positive or negative effect (though this may be because this issue has not been examined in the clinic with any degree of rigor). Tamsulosin, the structurally dissimilar sulphonamide and the most recently introduced member of the alpha-blocker class,
has a somewhat unique profile. Several large clinical studies show that tamsulosin can produce ‘abnormal’ ejaculation in up to 30% of patients, depending on dose.\(^\text{13}\) As there is little evidence of changes in ejaculatory function to this extent with alfuzosin, doxazosin, prazosin, or terazosin, it is unlikely that this is a class effect for all alpha-blockers. Although several studies have attempted to determine the underlying mechanism of action, results have been equivocal and are often contradictory. What is clear is that the abnormal ejaculation cannot be accounted for by the receptor-binding profile of tamsulosin across the three alpha-1-adrenoceptor subtypes; its profile on the three subtypes is not different from that of the quinazoline alpha-blockers to an extent that could account for such a major clinical difference, either with respect to efficacy or the ejaculatory dysfunction. The favored view is that tamsulosin has an additional action, over the same concentration range (in the test tube and animals), or dose range (in the clinic), at dopamine and serotonin receptors.\(^\text{14}\) The laboratory and animal data linking both systems to ejaculatory function is to a certain extent supported by clinical data, in particular, from large phase 3 studies in over 1200 subjects, in which the modified selective serotonin reuptake inhibitor (SSRI) dapoxetine, increases ejaculation latency albeit in patients with premature ejaculation.\(^\text{15}\) Although not formally evaluated to the same extent as dapoxetine several SSRIs are widely used ‘off-label’ as front-line therapy for premature ejaculation (see Chapter 62). An action on central serotoninergic pathways could well translate into a change in ejaculatory function. Likewise, some anecdotal clinical data suggesting that the dopamine partial agonist apomorphine increases the force of ejaculation would be consistent with an interaction between tamsulosin and dopamine receptors, accounting for the observed abnormal ejaculation. In radioligand-binding studies and in the rat in vivo, tamsulosin has been shown to interact with both dopamine and serotonin receptors. Ironically, determination of the precise pharmacological basis for tamsulosin’s action on the ejaculatory reflex could lead to the development of novel therapy for the treatment of either premature ejaculation or retarded ejaculation.

The potential of phosphodiesterase type 5 inhibitors in treating lower urinary tract symptoms

The history and clinical efficacy of PDE-5 inhibitors in the treatment of ED has been well documented since the arrival of sildenafil onto the marketplace a decade ago (see Chapters 30–32). Not surprisingly, being the prototype of a new mechanistic class, sildenafil and its more recent clones, tadalfil and vardenafil, have been subsequently more widely evaluated for other potential clinical utilities; indeed PDE-5 inhibitors are now also approved in several countries for the treatment of pulmonary hypertension.

The PDE-5 isozyme is fairly widely and yet discretely distributed within the urogenital sinus. This is covered in much more detail in Chapter 28. Perhaps not surprisingly, therefore, several preclinical and clinical studies have been undertaken on the impact of PDE-5 inhibitors on bladder, prostatic and urethral function. Of particular interest are the studies relating to LUTS. The potential therapeutic applications for BPH and urinary urge incontinence were first recognized by Pfizer in the form of a patent as far back as 1999;\(^\text{16}\) part of the experimental evidence offered, in addition to PDE-5 isozyme location, was the finding of inhibition of spontaneous myogenic activity in strips prepared from unstable human detrusor muscle. This was followed relatively quickly by clinical support in the form of a (now largely ignored) study conducted in 2000 in the UK in BPH patients and published in 2002\(^\text{17}\) and followed by several additional studies in both BPH and ED patients. Although the original study was not using end-points now considered de rigueur, the findings were essentially similar to the much more comprehensive studies conducted several years later.\(^\text{18}\)

In general within the urogenital sinus the sympathetic nervous system and the NO-dependent non-adrenergic non-cholinergic (NANC) systems act in opposition (Figure 18.2). On that basis one would have anticipated that PDE-5 inhibitors would have the profiles of functional alpha-blockers (i.e. activation of NANC would be equivalent to blocking the sympathetic nervous system). In one key study, sildenafil has been shown to increase vascular perfusion in the prostate.
which is consistent with its general vasoactivity in vascular resistance vessels. In physiological terms, such a profile would be indistinguishable from that of an alpha-blocker. Given this potential functional equivalence, PDE-5 inhibitors would be expected to have a similar clinical profile to alpha-blockers such as alfuzosin and doxazosin and, based on the human in vitro work (see above), perhaps to have a greater effect on irritative symptomatology. In several well-designed clinical trials, it has become apparent that although there is a clinically significant effect on IPSS there is either little or no accompanying urodynamic change and, where there is such a change, it is not correlated with changes in symptoms. Overall the degree of improvement in IPSS was equivalent to that of alpha-blockers but, importantly from the point of view of clinical benefit, reached the level (>3) considered to be likely to be perceived by patients as an advantage. The limitations of the IPSS, designed to capture the overall LUTS symptom complex rather than individual components, preclude the drawing of any meaningful conclusion about a preferential effect on irritative versus obstructive symptoms. Although the overall clinical profile was not quite as expected, the degree of symptomatic improvement was encouraging and would appear to warrant further clinical evaluation.

The precise relationship between LUTS and ED is receiving increasing attention because both are common, are often co-associated, and have considerable impact on quality of life. As summarized elsewhere, there is evidence of potential pathophysiology linking both dysfunctions. The most intriguing concepts based on the vascular activity of drugs effective in both LUTS and ED, is that the clinical manifestations could be secondary to local ischemia within the target organs. Paradoxically, it seems that alpha-blockers, which appear to improve vascular perfusion within the bladder, also improve uroflow in BPH patients whereas PDE-5 inhibitors, which affect prostatic vascular perfusion, do not.

Overall, however, it remains unlikely that the observed clinical benefit of PDE-5 inhibitors in LUTS is secondary to the psychological impact of improving erectile function. Further evidence for a direct action on the organs associated with LUTS is that there is no absolute correlation between improvement in IIEF and improvement in IPSS.

In the future, there may be certain situations, particularly in patients with comorbid BPH and ED, in which PDE-5 inhibitor monotherapy could have a role to play in a holistic approach to managing the BPH patient. However, it should be remembered that no PDE-5 inhibitor is approved by the regulators for treating BPH and also that there could be considerable cost implications of daily PDE-5 inhibitor administration.

Cost considerations would also seem to rule out widespread use of combination therapy with alpha-blockers and PDE-5 inhibitors, as would the potential for augmentation of vascular side-effects. For these reasons, the clinical utility of PDE-5 inhibitors, to a large extent predictable from the basic molecular and pharmacological activities, may not progress beyond being of academic interest.

Summary

Many BPH patients have comorbid LUTS and ED, which should be taken into consideration in the selection of appropriate therapy. Several of the drugs used in the treatment of LUTS can have an adverse event on sexual function (e.g. finasteride, dutasteride, and tamsulosin). Most of the other approved alpha-blockers have little effect on sexual function (prazosin and terazosin) or may have slightly beneficial effects (alfuzosin and doxazosin).

As might have been anticipated from isozyme distribution studies and their action as functional sympatholitics, the PDE-5 inhibitor class does have a beneficial effect on LUTS. Paradoxically, the improvement in LUTS is achieved in the absence of any obvious urodynamic changes. Although it is tempting to conclude that PDE-5 inhibitors may become the therapy of choice for the many men with comorbid LUTS and ED, cost considerations may preclude this. The cost of regulatory approval may prove an additional deterrent to pharmaceutical companies. As such, a branded PDE-5 inhibitor may never reach the market place as approved therapy for the treatment of BPH. We may have to wait until the first generic PDE-5 inhibitor arrives to circumvent cost concerns.

REFERENCES


19 Basic assessment of the patient with erectile dysfunction

Roger S Kirby and Michael G Kirby

Introduction

Erectile dysfunction (ED) has traditionally been one of those hidden conditions that has been ignored by patients and doctors alike. With the progressive increase in life expectancy, and with the increasing quality of health and life in older people, the number of men who suffer from ED is ever increasing. The advent of effective oral therapy and the publicity that surrounded it brought ED into the public domain in a way that it had never been before, and as a result there are increasing numbers of men seeking treatment.

Traditionally therapy for ED was the domain of hospital specialists but it is increasingly clear that many men are best managed in the community either by primary care physicians or by nurse specialists. Although therapy in the community is clearly desirable, there are a number of issues that have thus far impeded such approaches. One of these issues is education.

Over the past two decades, knowledge of the pathogenesis of ED has expanded considerably and, with this, there has been a parallel increase in the variety and complexity of investigations employed to establish the cause of the disorder in the individual patient. However, despite the highly technological diagnostic modalities now available, the basic principle taught to every medical student – and one that is especially important in the evaluation of the man suffering from ED – must not be forgotten: that accurate diagnosis depends on a careful history and physical examination, the results of which are supplemented by tailored special investigations. Subsequent chapters dwell in some depth on the still evolving and increasingly sophisticated modalities of diagnosis used in ED, but in this chapter the question of how the patient and his partner should be initially assessed is addressed.

History

Because of the sensitive nature of the complaint of ED, it is of paramount importance to establish a relationship of trust between patient and clinician at an early stage. Building this rapport requires more time and patience than is usually required in, for example, the assessment of a patient with benign prostatic enlargement, and appointment schedules need to be adjusted accordingly. Recently, several formal symptom scores have been developed and validated, which aim to quantify the extent of ED. The two with the greatest facility are those developed by O’Leary et al.1 and by Rosen et al.2 (Tables 19.1 and 19.2).

Although such questionnaires are undoubtedly valuable, they do focus exclusively on the functional element of ED. A more complex question is the extent to which sexual dysfunction affects the quality of life; recently, Wagner et al. addressed this important issue.3 Their questionnaire, developed following interviews with patients presenting with ED both in the UK and the USA, is set out in Table 19.3.

The sexual experience questionnaire4 (Table 19.4) is a new instrument to assess patient-reported outcomes recording function, health-related quality of life, and satisfaction. Notwithstanding the value of these questionnaires, it is often helpful to start a face-to-face interview with a brief explanation of the distinction between loss of libido, ED, and ejaculatory disturbance. By far the most common presenting complaint is that of reduced rigidity of erections; less commonly, the patient complains of a total absence of erectile activity. Inadequate erection hardness will result in penile buckling or curving of the erection column about its neutral axis and thus failure of penetration and the inability to achieve successful intercourse. Quantitative assessment of erection hardness in the clinical setting offers physicians a brief and easy means of monitoring response to ED therapy.5

Enquiry should concentrate initially on this element of the symptoms and their duration, as well as on the rapidity and particular circumstances of onset. A key question is obviously whether the impairment of erections is consistent, rather than ‘situational’ with preservation of nocturnal and early-morning erections. Although the majority of physicians are now acquainted with the loose association between preservation of the nocturnal and early-morning erections and psychogenic impotence, most patients do not make this connection. A useful guide to the severity of the problem is to enquire when penetrative intercourse was last possible – not uncommonly the surprising reply is received, that this was accomplished only a few days ago!

Discreet enquiry should also be made as to whether the problem is confined to sexual encounters with one partner or whether it is also present with other partners. The partner’s attitude to the potency problem should also be established. Questions about deviant sexual behavior or taboo practices at this early stage, although relevant, risk compromising the developing relationship between interviewer and patient.
Table 19.1 A brief sexual function inventory. (From ref. 1, with permission)

<table>
<thead>
<tr>
<th>SEXUAL DRIVE</th>
<th>Let’s define sexual drive as a feeling that may include wanting to have a sexual experience (masturbation or intercourse), thinking about having sex or feeling frustrated due to lack of sex.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. During the past 30 days, on how many days have you felt sexual drive?</td>
<td>No days</td>
</tr>
<tr>
<td>2. During the past 30 days, how would you rate your level of sexual drive?</td>
<td>None at all</td>
</tr>
<tr>
<td>ERECTIONS</td>
<td></td>
</tr>
<tr>
<td>3. Over the past 30 days, how often have you had partial or full sexual erections when you were sexually stimulated in any way?</td>
<td>Not at all</td>
</tr>
<tr>
<td>4. Over the past 30 days, how often have you had erections; how often were they firm enough to have sexual intercourse?</td>
<td>0</td>
</tr>
<tr>
<td>5. How much difficulty did you have getting an erection during the last 30 days?</td>
<td>Did not get erections at all</td>
</tr>
<tr>
<td>EJACULATION</td>
<td></td>
</tr>
<tr>
<td>6. Over the past 30 days, how much difficulty have you had in ejaculating when you have been sexually stimulated?</td>
<td>Have had no sexual stimulation in past month</td>
</tr>
<tr>
<td>7. In the past 30 days, how much did you consider the amount of semen you ejaculate?</td>
<td>Did not climax</td>
</tr>
<tr>
<td>PROBLEM ASSESSMENT</td>
<td></td>
</tr>
<tr>
<td>8. In the past 30 days, to what extent have you considered a lack of sex drive to be a problem?</td>
<td>Big problem</td>
</tr>
<tr>
<td>9. In the past 30 days, to what extent have you considered your ability to get and keep an erection a problem?</td>
<td>0</td>
</tr>
<tr>
<td>10. In the past 30 days, to what extent have you considered your ejaculation to be a problem?</td>
<td>0</td>
</tr>
<tr>
<td>OVERALL SATISFACTION</td>
<td></td>
</tr>
<tr>
<td>11. Overall, during the past 30 days, how satisfied have you been with your sex life?</td>
<td>Very dissatisfied</td>
</tr>
</tbody>
</table>

Although libido is usually preserved in men presenting with ED, inevitably increasing the psychological frustrations of the patient, a decline of sexual drive may suggest an endocrinological cause of the problem and this should be carefully documented. Ejaculation is much less commonly affected than erection itself, but enquiry should be made as to whether ejaculation is premature, delayed, dry (as commonly occurs following transurethral resection of the prostate), or absent altogether.

The previous medical history should include a brief survey of sexual history, which may provide a clue to a congenital problem, due perhaps to a veno-occlusive disorder or congenital chordee. Previous surgery, especially pelvic surgery for bowel, bladder, or prostatic malignancy, reconstructive vascular surgery, or renal transplantation, may obviously be relevant. Multi-system disorders may result in impotence and can sometimes present with this symptom. Hypertension and diabetes mellitus are by far the most common of these
Table 19.2  Individual items of International Index of Erectile Function (IEF) Questionnaire and response options (US version). (From ref. 2, with permission).

<table>
<thead>
<tr>
<th>Question*</th>
<th>Response options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1: How often were you able to get an erection during sexual activity?</td>
<td>0 = No sexual activity &lt;br&gt; 1 = Almost never/never</td>
</tr>
<tr>
<td>Q2: When you had erections with sexual stimulation, how often were your erections hard enough for penetration?</td>
<td>2 = A few times (much less than half the time) &lt;br&gt; 3 = Sometimes (about half the time) &lt;br&gt; 4 = Most times (much more than half the time) &lt;br&gt; 5 = Almost always/always</td>
</tr>
<tr>
<td>Q3: When you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?</td>
<td>0 = Did not attempt intercourse &lt;br&gt; 1 = Almost never/never</td>
</tr>
<tr>
<td>Q4: During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?</td>
<td>2 = A few times (much less than half the time) &lt;br&gt; 3 = Sometimes (about half the time) &lt;br&gt; 4 = Most times (much more than half the time) &lt;br&gt; 5 = Almost always/always</td>
</tr>
<tr>
<td>Q5: During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?</td>
<td>0 = Did not attempt intercourse &lt;br&gt; 1 = Extremely difficult &lt;br&gt; 2 = Very difficult &lt;br&gt; 3 = Difficult &lt;br&gt; 4 = Slightly difficult &lt;br&gt; 5 = Not difficult</td>
</tr>
<tr>
<td>Q6: How many times have you attempted sexual intercourse?</td>
<td>0 = No attempts &lt;br&gt; 1 = One to two attempts &lt;br&gt; 2 = Three to four attempts &lt;br&gt; 3 = Five to six attempts &lt;br&gt; 4 = Seven to ten attempts &lt;br&gt; 5 = Eleven + attempts</td>
</tr>
<tr>
<td>Q7: When you attempted sexual intercourse, how often was it satisfactory for you?</td>
<td>0 = Did not attempt intercourse &lt;br&gt; 1 = Almost never/never &lt;br&gt; 2 = A few times (much less than half the time) &lt;br&gt; 3 = Sometimes (about half the time) &lt;br&gt; 4 = Most times (much more than half the time) &lt;br&gt; 5 = Almost always/always</td>
</tr>
<tr>
<td>Q8: How much have you enjoyed sexual intercourse?</td>
<td>0 = No intercourse &lt;br&gt; 1 = No enjoyment &lt;br&gt; 2 = Not very enjoyable &lt;br&gt; 3 = Fairly enjoyable &lt;br&gt; 4 = Highly enjoyable &lt;br&gt; 5 = Very highly enjoyable</td>
</tr>
<tr>
<td>Q9: When you had sexual stimulation or intercourse, how often did you ejaculate?</td>
<td>0 = No sexual stimulation/intercourse &lt;br&gt; 1 = Almost never/never</td>
</tr>
<tr>
<td>Q10: When you had sexual stimulation or intercourse, how often did you have the feeling of orgasm or climax?</td>
<td>2 = A few times (much less than half the time) &lt;br&gt; 3 = Sometimes (about half the time) &lt;br&gt; 4 = Most times (much more than half the time) &lt;br&gt; 5 = Almost always/always</td>
</tr>
<tr>
<td>Q11: How often have you felt sexual desire?</td>
<td>1 = Almost never/never &lt;br&gt; 2 = A few times (much less than half the time) &lt;br&gt; 3 = Sometimes (about half the time) &lt;br&gt; 4 = Most times (much more than half the time) &lt;br&gt; 5 = Almost always/always</td>
</tr>
<tr>
<td>Q12: How would you rate your level of sexual desire?</td>
<td>1 = Very low/none at all &lt;br&gt; 2 = Low &lt;br&gt; 3 = Moderate &lt;br&gt; 4 = High &lt;br&gt; 5 = Very high</td>
</tr>
</tbody>
</table>

*All question are preceded by the phrase “Over the past 4 weeks”.

(Continued)
Table 19.2  Continued

<table>
<thead>
<tr>
<th>Question*</th>
<th>Response options</th>
</tr>
</thead>
</table>
| Q13: How satisfied have you been with your overall sex life? | 1 = Very dissatisfied  
2 = Moderately dissatisfied  
3 = About equally satisfied and dissatisfied  
4 = Moderately satisfied  
5 = Very satisfied |
| Q14: How satisfied have you been with your sexual relationship with your partner? |
| Q15: How do you rate your confidence that you could get and keep an erection? | 1 = Very low  
2 = Low  
3 = Moderate  
4 = High  
5 = Very high |

*All questions are preceded by the phrase “Over the past 4 weeks”.

Table 19.3  QOL-MED questionnaire: item list

1. I feel frustrated because of my erection problem
2. My erection problem makes me feel depressed
3. I feel like less of a man because of my erection problem
4. I have lost confidence in my sexual ability
5. I worry that I won’t be able to get or keep an erection
6. My erection problem is always on my mind
7. I feel that I have lost control over my erections
8. I blame myself for my erection problem
9. I feel angry because of my erection problem
10. I worry about the future of my sex life
11. I have lost pleasure in sex because of my erection problem
12. I am embarrassed about my problem
13. I worry about being humiliated because of my problem
14. I try to avoid having sex
15. I feel different from other men because of my erection problem
16. I get less enjoyment out of life because of my erection problem
17. I feel guilty about my erection problem
18. I am afraid to ‘make the first move’ towards sex
19. I worry that my partner blames herself for my erection problem
20. I worry about letting her down because of my erection problem
21. I worry that I’m not satisfying her because of my erection problem
22. I worry that we are growing apart because of my erection problem
23. I worry that she is looking for someone else because of my problem
24. I feel that she blames me for my erection problem
25. I worry that she thinks I don’t want her because of my erection problem
26. I have trouble talking to her about my problem
27. My erection problem interferes with my daily activities

(Reproduced from ref. 3 with permission.)

(and the family history may provide a clue), but alcoholism, thyroid dysfunction, hemochromatosis, and other systemic disorders should be borne in mind (Table 19.6).

Of the neurological disorders that may cause ED, multiple sclerosis is the most frequently encountered, but ED is seldom a presenting feature of the disease. Another diffuse disease affecting the central nervous system, however, may produce ED as its earliest presenting manifestation: this disease, originally known as the Shy–Drager syndrome but now more commonly termed multiple system atrophy (MSA), is characterized by selective degeneration of autonomic neurons in the central nervous system (CNS). In this disorder there is progressive selective cell loss from the pons, medulla, and cerebellum, as well as degeneration of the neurons of the intermediolateral cell column of the thoracolumbar sympathetic outflow and sacral parasympathetic outflow (Figure 19.1). The condition affects patients in their middle age, with a male–female ratio of 2:1. In the male, ED is accompanied by frequency and urgency of micturition, which may be confused with bladder outflow obstruction resulting from benign prostatic enlargement. An important sign that may provide a clue to this sometimes elusive diagnosis is postural (orthostatic) hypotension, caused by impaired sympathetic vasoconstrictor tone, and this can usually be demonstrated on measuring blood pressure in the standing and lying positions.

The vascular endothelium provides the source of the critical association between ED and cardiovascular events, because it plays a vital role in regulation of the circulation. Hyper- tension, ischemic heart disease, and hypercholesterolemia can all lead to abnormalities of the vascular smooth muscle cells and the extracellular matrix. This endothelial cell dysfunction can precede the formation of atherosclerotic plaques and is common in cardiovascular disease (CVD) and diabetes. Patients with diabetes have endothelial dysfunction and an increased risk of developing cardiovascular complications. Impaired endothelium-dependent vasodilatation via nitric oxide (NO) is also well documented in coronary artery disease and in conditions such as diabetes, hypertension, and dyslipidemia.

ED can also provide an important measure of CVD progression and severity. For example, patients with single-vessel
Table 19.4 Sexual experience questionnaire (Sex-Q)\(^4\)

**Instructions**
For each of the following questions, place an 'X' in the one box that best describes your answer.

**Over the past 4 weeks**

1. How often were you able to maintain an erection for as long as you wanted to?
   - Never or almost never
   - Rarely
   - Sometimes
   - Usually
   - Always or almost always

2. During sexual intercourse, how often were you able to penetrate your partner?
   - Never or almost never
   - Rarely
   - Sometimes
   - Usually
   - Always or almost always

3. How much have you worried about whether you could get an erection?
   - Not at all worried
   - A little worried
   - Somewhat worried
   - Very worried
   - Extremely worried

4. How confident were you that you could get an erection when you wanted to?
   - Not at all confident
   - A little confident
   - Somewhat confident
   - Confident
   - Very confident

5. How satisfied were you with the hardness of your erections?
   - Very dissatisfied
   - Dissatisfied
   - Equally satisfied and dissatisfied
   - Satisfied
   - Very satisfied

6. How satisfied were you with the duration of your erections?
   - Very dissatisfied
   - Dissatisfied
   - Equally satisfied and dissatisfied
   - Satisfied
   - Very satisfied

7. How satisfied were you with your level of sexual desire?
   - Very dissatisfied
   - Dissatisfied
   - Equally satisfied and dissatisfied
   - Satisfied
   - Very satisfied

8. How satisfied were you with your overall sexual activity?
   - Very dissatisfied
   - Dissatisfied
   - Equally satisfied and dissatisfied
   - Satisfied
   - Very satisfied

9. How much pleasure did you get from sexual activity?
   - No pleasure
   - Little pleasure
   - Some pleasure
   - Much pleasure
   - Great pleasure

10. How confident were you that you could satisfy your partner during sexual activity?
    - Not at all confident
    - A little confident
    - Somewhat confident
    - Confident
    - Very confident

11. How often did you achieve mutual satisfaction with your partner?
    - Never or almost never
    - Rarely
    - Sometimes
    - Usually
    - Always or almost always

12. How satisfied were you with your ability to control the timing of your ejaculations?
    - Very dissatisfied
    - Dissatisfied
    - Equally satisfied and dissatisfied
    - Satisfied
    - Very satisfied
Basic assessment of the patient with erectile dysfunction

Table 19.5  Erection hardness score

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Penis does not enlarge</td>
</tr>
<tr>
<td>1</td>
<td>Penis is larger but not hard</td>
</tr>
<tr>
<td>2</td>
<td>Penis is hard but not hard enough for penetration</td>
</tr>
<tr>
<td>3</td>
<td>Penis is hard enough for penetration but not completely hard</td>
</tr>
<tr>
<td>4</td>
<td>Penis is completely hard and fully rigid</td>
</tr>
</tbody>
</table>

How would you rate the hardness of your erection?

Table 19.6  Organic causes of erectile dysfunction

<table>
<thead>
<tr>
<th>Congenital deformities</th>
<th>Epispadias</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hypospadias</td>
</tr>
<tr>
<td></td>
<td>Congenital chordee</td>
</tr>
<tr>
<td></td>
<td>Microphalus</td>
</tr>
<tr>
<td>Mechanical</td>
<td>Morbid obesity</td>
</tr>
<tr>
<td></td>
<td>Peyronie’s disease</td>
</tr>
<tr>
<td></td>
<td>Bilateral hydrocele</td>
</tr>
<tr>
<td></td>
<td>Phimosis</td>
</tr>
<tr>
<td></td>
<td>Tethered frenulum</td>
</tr>
<tr>
<td></td>
<td>Carcinoma of penis</td>
</tr>
</tbody>
</table>

| Postsurgical           | Cystectomy, urethrectomy |
|                       | Radical prostatectomy |
|                       | Abdominoperineal resection of rectum |
|                       | Low anterior resection of rectum |
|                       | Rectal pull-through procedures |
|                       | Transurethral resection of prostate |
|                       | External sphincterotomy |

| Vascular insufficiency | Aorta-iliac disease (Leriche syndrome) |
|                       | Internal iliac atheroma |
|                       | Atheroma of pudendal vessels |
|                       | Distal vessel disease |
|                       | Post-priapism |
|                       | Smoking |
|                       | Anemia |
|                       | Veno-occlusive dysfunction |
|                       | Post-pelvic fracture |

| Metabolic disorders    | Diabetes mellitus |
|                       | Hemochromatosis |
|                       | Alcoholism |
|                       | Sickle-cell disease |
|                       | Hepatic/renal failure |
|                       | Scleroderma |
|                       | Thyroid disease |
|                       | Adrenal disease |

| Neurogenic disorders   | Multiple system atrophy |
|                       | Spinal cord lesions |
|                       | Multiple sclerosis |
|                       | Tabes dorsalis |
|                       | Peripheral neuropathies |
|                       | Spina bifida |
|                       | Amyotrophic lateral sclerosis |

Table 19.6  Continued

<table>
<thead>
<tr>
<th>Abnormalities of hypothalamopituitary function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital</td>
</tr>
<tr>
<td>LH-FSH deficiency (Kallmann’s syndrome)</td>
</tr>
<tr>
<td>Congenital hypogonadotrophic hypogonadism</td>
</tr>
<tr>
<td>Panhypopituitarism</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Acquired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trauma, infiltrative disease, tumors of pituitary, etc.</td>
</tr>
<tr>
<td>Exogenous hormones</td>
</tr>
<tr>
<td>Hyperprolactinemia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary gonadal abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromosomal abnormalities (e.g. Klinefelter’s syndrome)</td>
</tr>
<tr>
<td>Bilateral anorchia</td>
</tr>
<tr>
<td>Gonadal toxins</td>
</tr>
<tr>
<td>Drug-induced gonadal damage (chemotherapeutic agents)</td>
</tr>
<tr>
<td>Gonadal injury (trauma/mumps/torsion)</td>
</tr>
</tbody>
</table>

Figure 19.1  A section through the spinal cord of a man who suffered from multiple system atrophy. There is selective loss of cell bodies from Onuf’s nucleus.

Ischemic heart disease have firmer erections and less difficulty in obtaining an erection than those patients with two- or three-vessel disease, the penis thereby acting as a barometer of cardiovascular status.

Early identification of coronary heart disease risk

A study of a group of healthy men complaining of ED found that 60% had abnormal cholesterol levels, and >90% showed evidence of penile arterial disease during Doppler ultrasound
imaging. In another study it was discovered that 80% of asymptomatic males with ED displayed at least one risk factor for CVD. Patients who subsequently underwent coronary angiography were found to have significant coronary artery disease, with over half diagnosed with multi-vessel disease. Therefore, routine investigations into the ED patient’s cardiovascular status can aid the identification of previously undiagnosed CVD.

Drug history

A detailed history of all concomitant medications is important in the evaluation of patients with ED, since many pharmacological agents may be associated with problems of potency (Table 19.7). Often, it is difficult to decide whether it is the drug itself or the condition for which it is being administered (e.g. hypertension) that has caused the symptom.

Antihypertensive agents have often been cited as the most common medication-related cause of ED. Clonidine, methyl-dopa, and reserpine, all of which share a centrally acting sympatholytic effect, are associated with an incidence of ED in about one-quarter to one-third of patients treated, but these agents are now seldom used therapeutically. The precise mechanism by which they impair potency is unclear, but they probably directly reduce libido by a central effect, and they may also elevate serum prolactin levels. Peripherally acting alpha-adrenoceptor blockers, such as phenoxybenzamine (which produces mixed alpha-1 and alpha-2 blockade) and the newer alpha-1-selective adrenoceptor blockers, prazosin, doxazosin, and terazosin, are less commonly associated with ED. In fact, from their vasodilator action on cavernosal vessels, one might expect their effect to be mildly beneficial. However, by blocking the sympathetically mediated closure of the bladder neck at the time of ejaculation, they may occasionally produce retrograde ejaculation. Indeed, the alpha-1A-selective adrenoceptor blocker tamsulosin seems to be particularly potent in this respect. In the Treatment of Mild Hypertension Study (TOMHS), most classes of antihypertensive agent (diuretic, beta-blocker, angiotensin-converting enzyme inhibitor, and calcium-channel blocker) were associated with a higher incidence of sexual dysfunction than placebo. By contrast, the alpha-1 adrenoceptor blocker doxazosin appeared less likely than placebo to produce this effect, suggesting a beneficial action of reduced alpha-1 adrenoceptor tone (Figure 19.2). The angiotensin receptor blocking drugs may have significant advantages. Fogari et al. have demonstrated that valsartan may have a beneficial effect on ED.

In other studies, beta-adrenoceptor blockers have often been reported to cause ED (especially at higher doses), directly by a peripheral action on the corporal tissue and also perhaps by a central effect on libido. Their ability to penetrate the CNS and induce a sympatholytic effect depends on their lipid solubility. Newer beta-blockers, such as atenolol, are less lipid-soluble and seem to cause less impairment of sexual function.

Diuretics have also been linked with ED: in particular, spironolactone has been reported to induce gynecomastia, ED, and reduced libido in some patients, and vasodilators such as hydralazine also seem to produce ED.
Clinical experience confirms that certain antihypertensive drugs affect not only the blood pressure, but also compliance of the erectile tissue, resulting in a functional venous leak. This may impair erectile function as much as arteriosclerotic changes of the vascular system secondary to hypertension.\(^1\)

It must be remembered that, in some patients with partial vasculogenic ED, high systolic arterial pressures may be required to achieve sufficient cavernosal artery flow for erection. Lowering blood pressure into the normal range in itself may, therefore, compromise penile blood flow to some extent and induce or exacerbate ED.\(^2\)

Many major and minor tranquilizers and hypnotics have been reported to cause both diminished libido and ED.\(^3\) Antidepressants such as monoamine oxidase inhibitors and tricyclic compounds may cause ED, probably by decreasing libido. The minor tranquilizers or anxiolytic agents, particularly the benzodiazepines, exert a depressive effect on the brainstem, limbic system and septal region; libido can also be reduced and ED may follow. Meprobamate, barbiturates, and other sedative hypnotics all exert a central effect similar to that of the benzodiazepines, with consequent effects on erectile function and libido.

Drugs with anti-androgenic activity, such as ketoconazole, cyproterone acetate, and the histamine receptor blocker cimetidine,\(^4\) are known to cause diminished potency; however, interestingly, bicalutamide and flutamide, which are pure anti-androgens, seem to spare, in relative terms, both potency and libido, while still effectively blocking androgen receptors. This effect has been suggested to be the result of elevated serum testosterone levels. The luteinizing hormone releasing hormone analogs, such as goserelin and leuprolide, induce medical castration and are almost always associated with ED, as well as with profound suppression of libido. By contrast, 5-alpha-reductase inhibitors produce ED and loss of libido in only 3–5% of patients.\(^5\) This suggests that testosterone, rather than its 5-alpha-reduced form dihydrotestosterone, is mainly responsible for the maintenance of erectile function and libido.

Recreational drugs such as marijuana and, especially, cocaine and heroin\(^6\) may also cause impotence and reduce libido, and are associated with a reduction of testosterone levels. Cigarette smoking, probably by virtue of its vasoconstricting effect or by the induction of atheroma, has also been reported to cause impaired potency.\(^7\) Alcoholism may induce ED by several mechanisms: these include peripheral neuropathy, testicular dysfunction, and an effect on the hypothalamic-pituitary axis, as well as impaired hepatic function resulting in increased serum estrogen levels.\(^8\) Even moderate doses of alcohol may impair erectile function (although, frustratingly, they also increase libido). As a consequence, patients with potency problems should usually be advised to reduce their alcohol consumption, as well as to refrain from cigarette, cigar, and pipe smoking.

### Physical examination

A thorough physical examination is an important part of the basic assessment of the man with ED; care should be taken to look for clinical signs of thyroid underactivity or overactivity, as well as stigmata of liver failure or anemia. Hypertension and other serious cardiovascular pathology must also be excluded. All peripheral pulses should be palpated and any cardiac murmurs or arrhythmias identified. A focused neurological examination is valuable, with special attention being paid to the sacral spinal outflow. Saddle anesthesia, with loss of bulbocavernous reflex in combination with a lax anal sphincter, may suggest the presence of an occult cauda equina lesion. This disorder may occasionally present with ED as a result of a central prolapse of an intervertebral disc or a slow-growing lumbar or sacral intraspinal tumor.

Examination of the external genitalia should be performed with a view to excluding congenital or acquired abnormalities of the penis itself. Peyronie’s plaques should be sought along the palpable length of the corpora, and the patient should be questioned about the presence of pain on intercourse or erectile deformity. Preputial abnormalities, such as tethering of the frenulum or phimosis, may occasionally present with ED, as may a spectrum of other genital abnormalities, including microphallus, episadias, and squamous cell carcinoma of the penis. The presence of small testes and reduced or absent secondary sexual characteristics may suggest hypogonadism, and it is worth enquiring about the frequency of necessity for facial shaving, as this may decline with androgen insufficiency. The anterior chest wall should be examined to exclude gynecomastia, and enquiry should be made about galactorrhea. Causes of primary hypogonadism and testicular failure are listed in Table 19.6; when any of these are present they
are usually an indication for referral for specialist endocrine opinion.

Digital rectal examination should be performed in men with ED to assess prostatic size and consistency. If the presence of benign prostatic enlargement is detected, a urinary flow rate should be determined and the patient warned that androgen therapy may risk exacerbation of bladder outflow obstruction. The presence of prostatic nodules should raise the possibility of early prostatic cancer and a prostate-specific antigen (PSA) value should usually be measured, at least in men over the age of 45. If the level of this marker is raised, a prostatic biopsy under transrectal ultrasound control may be necessary; in these circumstances, androgen replacement therapy is contraindicated, at least until adenocarcinoma of the prostate is excluded.

Special investigations

Investigation of the male patient with ED must, obviously, be tailored specifically to the individual concerned and any leads given by the history or examination. Baseline hematological and biochemical screens are necessary, which should exclude diabetes mellitus. Also included are liver function tests to exclude hepatic impairment, which may be associated with increased serum estrogen levels and reduced plasma testosterone. The baseline values are also useful if papaverine or hormone-replacement therapy is subsequently employed, because of the occasional hepatotoxicity associated with these treatments.

Estimation of serum hormone levels is expensive, and some investigators suggest that a single measurement of serum testosterone is all that is required. In occasional cases of hyperprolactinemia, however, serum testosterone may be just within normal limits, and a space-occupying lesion of the pituitary fossa (Figure 19.3) is obviously something that must not remain undetected. Many clinicians dealing with ED routinely measure testosterone, prolactin, and sex hormone-binding globulin. Patients with significant abnormalities of serum testosterone or prolactin levels often respond well to treatment. As discussed previously, a PSA value should be obtained to assess the probability of the patient harboring an incidental prostate carcinoma.

While sophisticated neurological testing is not possible in the office setting and there are currently no accurate methods for testing the autonomic nerve supply to the genitalia, biothesiometry is an accurate measure of peripheral sensation and can be applied to the penis (Figure 19.4). The biothesiometer tests vibratory sensation and can be compared with a normal age-adjusted nomogram for standardization (Figure 19.5). The sensation is first tested on the index fingers by applying the vibrating wand lightly and increasing vibration frequency with the rheostat until first sensation. The procedure is repeated on the inner thighs, penile shaft, and finally the glans penis. Patients with peripheral neuropathy, penile nerve damage, and Peyronie’s disease will exhibit reduced sensation for age.

Often, the most valuable information obtained in an outpatient or office setting is the assessment of response to intracavernosal prostaglandin E-1 (PGE-1). Although some clinicians withhold this diagnostic test until the second visit, it is often convenient to employ a small test dose (1.25–2.5 µg) on the first attendance. Prior to administration of this compound, the patient must be warned about the possibilities of bruising (which is of little significance) and of a prolonged response (>6 hours), which must be treated by corporal aspiration or intracorporal phenylephrine or other alpha-adrenergic injection within 6–8 hours. A signed consent form is useful, as well as a detailed description of whom to contact.
and what to do should the erection fail to disappear spontaneously. An absent or impaired response may be an indication for color Doppler scanning of the cavernosal and dorsal penile arteries, with higher dosage of PGE-1 to exclude arterial insufficiency or venous leakage. This investigation is indicated in patients in whom reconstruction would be considered, and it can be arranged before the second consultation. Further details of this and other special investigations for elucidating the cause of impaired erectile potency are discussed in greater detail in subsequent chapters. In particular, Chapter 33 is relevant, since there is increasing evidence that ED may act as a harbinger of a cardiovascular event caused by more widespread atherosclerosis. More intensive testing to establish cardiovascular risk may therefore be indicated.

The second Princeton consensus on sexual dysfunction and cardiac risk stated that the recognition of ED as a warning sign of silent vascular disease has led to the concept that a man with ED and no cardiac symptoms is a cardiac (or vascular) patient until proved otherwise. Men with ED and other cardiovascular risk factors should be counseled in lifestyle modification.

**Conclusion**

The initial basic assessment of ED is of some importance, because it is the main opportunity for the clinician to establish a rapport with the patient. This first meeting, if effectively and sympathetically handled, can set this relationship on the course towards a successful outcome for the patient, the doctor, and the partner.

With the advent of new, effective, non-invasive therapies, such as intra-urethral PGE-1 and the phosphodiesterase type 5 inhibitors (sildenafil, vardenafil, and tadalafl) the history and examination have assumed an even more important role in ED, since many patients will wish to start therapy without proceeding with invasive investigations. However, the importance of excluding other important pathologies, such as diabetes mellitus, hypertension, or pituitary tumor, should not be underestimated. Many of the issues raised in this chapter are addressed more extensively in subsequent chapters; however, as in most other areas of life, the need for special care and attention to detail at the outset of the process of diagnosis and treatment remains paramount.

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**REFERENCES**

Introduction and background

Advances in our understanding of which men develop sexual problems is a fairly recent phenomenon, aided by several large population-based studies, such as the Massachusetts Male Aging Study and the Global Study for Attitudes and Behaviors.1–4 It can, however, be argued that the modern age of erectile dysfunction (ED) management began with the refined knowledge of the physiology of erection, based on the landmark studies from Krane, Goldstein, Lue and others in the 1980s using animal models and human volunteers.5–8 These studies investigated the cellular basis of erectile function and allowed for a greater appreciation of the fundamental role played by relaxation of the cavernous smooth muscle in initiating and maintaining erection. Early work in dog and monkey models demonstrated the essential vascular nature of erection and the control mechanisms that fail in dysfunction. Subsequently proven in humans, the findings of these studies served as the trigger that led to the development of multiple agents delivered through an intracavernous approach able to restore erectile function to men with neurogenic and vascular causes of their ED.9

Among the most dramatic advances in ED management at that time was the ability to visualize the vascular deficiency in ‘real time’ with equipment that was present in most large hospitals and peripheral clinics. The ability to visualize peak cavernosal arterial pulse waves and determine the extent of vascular insufficiency by means of duplex scanning was an eye opener to clinicians (Figure 20.1). The duplex scanner was a quantum leap forward and proved to be an approach that rapidly gained worldwide acceptance. Within a decade of its first description,10,11 duplex Doppler penile ultrasound scanning became an essential minimally invasive component of many ED assessment approaches. Technological improvements in equipment, the advent of color Doppler, and power Doppler further added to the utility of these imaging machines. Researchers worldwide using duplex scanners reported on age-specific flow rates, novel diagnostic protocols, and clinical scenarios in which ultrasound scanning was clinically essential.12–20

The discovery and subsequent approval of phosphodiesterase type 5 (PDE-5) inhibitors for ED in the late 1990s made vascular testing less relevant.21 Most clinicians recognized rapidly that, although imaging provided information to the patient and clinician, in most cases no change in management resulted, and the golden age of duplex scanning passed. Additionally, the reproducibility of duplex results was questioned.22,23 Cost, the reality that PDE-5 inhibitors would be effective regardless of the etiology of ED, and the development of goal-oriented treatment algorithms that eliminated a diagnosis as an essential part of the management approach all limited the role of ultrasound in ED.24

Over the past decade a refined approach has developed towards imaging in sexual medicine. Duplex Doppler ultrasound has proven its utility in predicting success for Peyronie’s reconstructive surgery and in defining the potential for reversibility of vascular insufficiency prior to proceeding to penile implantation.25–28 Use of ultrasound scanning in cases of priapism to define high flow or low flow is without question.29,30 Although the surgical management of venous leak remains dubious, demonstration of high-end diastolic flow remains a reliable indicator of veno-occlusive dysfunction and frequently serves as the initial screening modality prior to the more invasive and costly testing with dynamic infusion cavernosometry and cavernosography.31–33 Penile fracture, subtle forms of Peyronie’s disease (including newly described variants) are often appreciated only with duplex scanning.34–36 Finally, among the population of men who wish to have a more complete understanding of the etiology of their condition, investigations like duplex Doppler remain essential. This indication has recently become more relevant as several reports have linked ED of vascular origin as a potential harbinger of future cardiovascular events. The ability to define the extent of arterial insufficiency particularly in young men, may provide clinicians with sufficient lead time (thought to be roughly 3 years) to modify risks and thus avoid strokes and myocardial infarcts.37–40

This chapter provides a critical contemporary review of current indications and utility for duplex scanning in sexual dysfunction.

Peyronie’s disease and variants

Although initially described more than 250 years ago, Peyronie’s disease remains an important clinical entity for physicians who treat it and for the 2–7% of men who are affected by this localized fibrosing condition. The classical description is one of a triphasic disease state, where initial pain transitions into penile deformity and subsequently stabilizes.41 Although the
true pathogenesis remains to be fully elucidated, many reports describe early trauma and a delaminating series of events generally related to sexual activity that lead to scarring of the tunica albuginea. The penile shape change relies on the normally compliant and elastic tunica albuginea becoming rigid, inducing a curve towards the scar with erection. The majority of men report a dorsal curve with a discrete palpable plaque. While only the most severely affected people generally proceed to surgical therapy, use of minimally invasive intravascular approaches with verapamil and interferon has increased the need for localization of the plaque and physiologic assessments of the penile anatomy. Novel approaches to diagnosis and management of Peyronie’s disease have evolved over the past few years, with proteomics – the measurement of altered protein patterns within the tunica layers with various stages of injury – being one. Peyronie’s disease may manifest itself in a large number of variations, impacting on the tunica at the periphery or within the septum (Figure 20.2).

Several decision points in managing men with Peyronie’s disease exist. Among those with disease requiring treatment, localization of the plaque is generally possible with palpation alone; however, subtle and evolving pathology may be realized only through imaging. Additionally, providing physiologic data on cavernosal arterial flow and end-diastolic flow as an indicator of veno-occlusive dysfunction compliments the history of erectile capacity. Among men with Peyronie’s disease who have poor erections, consideration of reconstruction is not recommended and a primary penile implant is our usual approach.

Recently, there have been a number of reports describing variants of Peyronie’s disease in which duplex scanning has been instrumental in their elucidation. Initially reported and published by our group and subsequently supported by publications from Tom Lue and his colleagues, intraseptal scars and discrete intra-penile injury may be detected in selected patients complaining of acute onset of pain. The ability to localize the pathology and provide objective evidence of the source of pain and deformity is often valued by the patients.

**Priapism**

Defined as persistent tumescence without sexual stimulation, priapism is generally classified into low-flow (veno-occlusive) and high-flow (arterial) forms. This distinction is an important one, since low-flow priapism is an ischemic process and a medical emergency whereas high-flow arterial priapism is not. Management algorithms rely on clinical history, measurement of intra-penile blood gases, and presenting complaints to determine the pathogenesis; however, use of duplex imaging is an integral component of evaluation in most cases.

While it is beyond the scope of this chapter to list the causes and conditions associated with veno-occlusive ischemic priapism, urgent diagnosis and treatment with alpha-agonists or shunting (or both) is essential to prevent long-term fibrosis and ED. Figure 20.3 demonstrates the extent of localized fibrosis that often results from extended periods of low-flow priapism.

The less common subtype of priapism, high-flow arterial priapism, is not a urologic emergency, and a complete evaluation using duplex scanning is often essential for optimal management. Recently, reports have demonstrated that this form of priapism is not as benign a condition as was initially thought, with the long-term incidence of ED being significant. The etiology is usually a small tear in the cavernosal artery as a consequence of penile straddle injury, in which the blunt trauma induces a flap and a high arterial fistula develops, with blood entering the cavernosal body without limitation by the resistance vessels. This induces a non-ischemic process in which tumescence without full rigidity exists.

The utility of the duplex scanner in this condition is without question. It provides for a diagnosis, localizes the side and exact extent of the injury, and facilitates embolization via angiography. Additionally, in cases in which smaller injuries can be identified, conservative management may be warranted.
The contemporary role of penile duplex scanning in sexual dysfunction

Penile fracture

This uncommon penile injury is most often reported as a consequence of direct axial pressure on an erect penis during intercourse, resulting in a tear of the fibroelastic tunica. Pain and a cracking sound are usually reported, with rapid hematoma formation at the site of injury. The tunica is thinnest at the lateral aspects and this is the most frequent anatomical location of the injury. Use of duplex scanning in cases of penile fracture has been reported. The ability to define the extent and location of the tunica albuginea tear and the state of the cavernosal artery are key aspects determining the management. Duplex scanning enables the disrupted tunica to be easily localized and visualization of other injuries, such as the spongiosum can also be assessed (Figure 20.4). Injury to the spongiosum, although not common, has been reported with penile fracture, and it generally involves more extensive pelvic injuries, as defined recently by Wessells et al., whose work has facilitated the prediction of spongiosal trauma following pelvic trauma.

Figure 20.2 (a) A dorsal scar in Peyronie’s disease in a cross-sectional view. (b) A peri-spongiosal scar located at the ventral aspect. (c) This septal scar was not palpable on digital exam in a young male patient complaining of penile pain but little deformity. (d) Punctate calcifications. These are often only detectable on imaging.

Figure 20.3 Corporal fibrosis following priapism. The ability to establish the extent of the penile scarring pre-operatively when a salvage implant is planned, can be essential in management.
Diagnosis of penile conditions with duplex scanning

Duplex scanning provides elegant pictures and clinically relevant information on the responsiveness of both the arterial and venous systems to vasoactive stimuli. Use of in-office vasoactive injection testing without imaging provides similar information without the ability to comment on whether mild-to-moderate vascular disease exists. This is an important evolving area of sexual medicine, since recent reports have linked early diagnosis of ED to future risks of cardiovascular events. The presence of arterial vascular pathology of the cavernosal system in younger men (aged 30–50 years) has been identified as an important independent risk factor for cardiovascular disease.\textsuperscript{12,54}

In an attempt to minimize the degree of invasiveness of Doppler investigations, researchers have described a wide range of protocols using oral PDE-5 inhibitors as the arterial activator coupled to direct visual sexual stimulation and self-stimulation. The classical approach of using intracavernous vasoactive agents provides for an assessment of the arterial and venous systems isolated from their neural axis. The ability to utilize oral agents is a breakthrough since it reduces the risk of priapism, pain, and tissue injury as a consequence of the intra-penile injection.\textsuperscript{31,51} Timing of the PDE-5 inhibitor should be optimized to allow scanning to be performed at the peak concentration of the agent, coupled to direct self-stimulation or visual sexual stimulation. At present the degree of standardization (normal values) and reproducibility with oral agents is not established to the same extent as it is with intracavernous injections.\textsuperscript{13,14,52}

Normative age-related cavernous artery flow rates have been described for men following intracavernous vasoactive injections.\textsuperscript{12} In general, peak arterial flows \(>30 \text{ cm/s}\) with resistive indices \(<0.8\) are considered normal. The ability to predict success for subsequent therapy has recently been reported and may further support the value of duplex scanning as part of the initial patient assessment in selected situations.\textsuperscript{53} The sensitivity of a well-conducted examination has been recently demonstrated through the ability to record changes in flow rate with improved health status.\textsuperscript{54} In situations in which vascular surgery (either arterial or venous) is being considered, a formal angiogram is appropriate. In most situations, however, the duplex scan provides adequate vascular testing.

A wide variety of protocols exists for duplex scanning in health and disease, although common themes across the many reports exist. Initial assessment for anatomical integrity is followed by evaluation of cavernous smooth muscle relaxation and determination of penile rigidity and deformity, if present (Table 20.1). Most protocols require between 10 and 60 minutes and may necessitate a second intra-penile injection or redosing of the PDE-5 inhibitor to ensure that maximum flow is measured, in an environment in which sympathetic tone does not adversely effect results.

Conclusions

Duplex scanning equipment appropriate for penile indications has advanced significantly over the past two decades since the original reports of its utility in diagnosing male ED were published. Currently, there exists a wide range of sexual concerns for which penile duplex scanning has value. Although initially described for use in determining cavernosal arterial flow as a means of arriving at a diagnosis, duplex scanning for this indication is less common today. The development of non-invasive therapies for sexual dysfunction has made the use of invasive diagnostic approaches less attractive as a component of the standard ED work-up.

Our enhanced understanding of the physiology of erection coupled to evolving therapeutic approaches for sexual dysfunction has altered the positioning of duplex imaging in ED management over the past decade. While goal-directed approaches for ED management remain the cornerstone of care described in most ED guidelines worldwide, with investigations
of etiology generally listed as optional, imaging remains an important tool for the specialist in selected situations. Duplex scanning remains clinically useful in:

- suspected high-flow priapism, to determine the site of injury and the side involved prior to angiographic embolization;
- in cases of penile trauma, to define the extent of penile fracture and to establish cavernosal artery integrity;
- in Peyronie’s disease and its several variants, to arrive at a diagnosis, to provide prognostic information, to define the extent of the disease, and to predict the likelihood of success;
- when penile prosthesis surgery for ED is planned, to assess arterial function and so rule out a reversible condition; and
- when greater understanding of the etiology is requested by the patient and his partner.

The future of duplex imaging in specialty erectile clinics in the management of the myriad of penile conditions outlined above remains bright. It is cost-efficient and often irreplaceable, directly altering treatment approaches. For these reasons it is likely to remain a vital tool for the busy specialist in sexual medicine in the years to come.

REFERENCES

21 Imaging in erectile dysfunction
David Rickards

Introduction
Vasculogenic causes account for up to 50% of erectile dysfunction (ED) patients. A number of techniques are available to investigate both the arterial and venous components of erection. Some have already fallen into disuse (e.g. the penile brachial index) and some have perhaps not achieved the popularity they deserve (e.g. radionuclide imaging). Color Doppler ultrasound imaging is widely used to investigate arterial inflow, cavernosometry is used to investigate venous drainage, and, more recently, magnetic resonance imaging (MRI) is being used to investigate underlying pathological conditions associated with ED. This chapter deals with cavernosometry and MRI.

In my unit, patient selection for these studies is made by the referring urologist or andrologist. The vast majority of patients have already been investigated by non-radiological studies and the implications of those are that a vasculogenic cause is likely.

Cavernosometry
Little has changed in this procedure since it was first described in the 1980s. It is invasive and painful and it utilizes ionizing radiation, contrast media, and vasoactive drugs. It is not a procedure to subject a patient to lightly, and only those who might benefit and would agree to undergo venous surgery should be considered. Modern urodynamic equipment usually comes with a dedicated cavernosometry program, which renders the procedure much safer because of pressure-sensitive pumps that prevent unduly high pressures being generated within the cavernosa. Cavernosometry is only performed once a penile Doppler has proved that there is no arterial insufficiency.

Technique
The patient is placed supine on a fluoroscopy table once the procedure has been explained and written consent has been given. To explain the procedure, the analogy of filling a bath is useful. To fill a bath, the taps are turned on and the plug inserted so the bath fills. The taps are the arteries, the plug the veins, and the bath the erectile tissues of the penis. In cavernosometry, it is whether or not the plug goes in that is being looked for and, in order to visualize potential leaks, contrast media is injected. First, however, the taps have to be turned on with an injection of a vasoactive drug into the side of the penis.

It is important to get the patient to relax as much as possible, since anxiety compromises erectile response. Such a situation is not easily obtained considering the invasiveness of the procedure. The distal two thirds of the penis are swabbed with antiseptic. Into one of the corpora cavernosa, an 18F butterfly needle is inserted at a point between the proximal two-thirds and the distal third of the penis. This is important because in the proximal penis there is a septum between the corpora, which is absent distally. This allows for bilateral perfusion of vasoactive drugs and contrast medium. Into the other corpus at the same level, a 21F needle is inserted. That the needles are correctly sited is evidenced by blood refluxing from them. If no blood is seen, a small amount of contrast can be injected under fluoroscopic control. If the needles are correctly sited, the contrast will be seen to flow easily from the tip of the needle. If not correctly sited, contrast will pool at the end of the needle and the patient will experience a sharp localized pain.

The 21F needle is connected to a pressure transducer and the larger 18F needle is attached to a 250 ml bottle of contrast medium (urographin 150) via a pump (Figure 21.1).

Through one of the needles, a vasoactive drug is injected, usually, prostaglandin E-1 20 µg, but other can be used, such as papaverine 30–60 mg or trimix, a combination of papaverine, phentolamine, and prostaglandin. Trimix should be used only if the other two agents produce no effect. The smaller 21F needle is flushed with saline and that it is recording pressures is confirmed by gently squeezing the penis. Immediately after the vasoactive drug has been injected, the pressure transducer is set to zero and the pressure is monitored and recorded. Once the vasoactive drug starts to take effect, the pressure within the corpora will start to rise. In pathological states, the pressure won’t rise very much because of the patient’s impotence. Once it has risen and stabilized, the pump is activated.

Modern cavernosal packages will increase the rate at which the pump instills contrast until a cavernosal pressure of 100 mmHg or 120 cm water is achieved. The pump will then automatically reduce its rate of infusion until a rate is found at which the cavernosal pressure is maintained at 100 mmHg.
Penile bruising is minimized by tight bandaging after the needles are removed. Contrast reactions are rare. Priapism can be expected in 10% of patients.

**Complications**

Penile bruising is minimized by tight bandaging after the needles are removed. Contrast reactions are rare. Priapism can be expected in 10% of patients.

**Magnetic resonance imaging**

MRI has been used to diagnose several penile disorders, including damaged erectile tissue caused by fracture or other
Anatomy and technique

The corpora and spongiosum are of intermediate to high signal intensity on T1-weighted sequences and high intensity on T2-weighted sequences. The spongiosum has similar signal intensity to that of the glans penis. High-resolution, small-field-of-view, thin-slice T2-weighted sequences with fat suppression in orthogonal planes using a surface coil are ideal. The penis should be taped to the anterior abdominal wall. Contrast enhanced scans are obtained using three-dimensional fat-saturated gradient echo volumes with 30 second acquisitions. All scans are performed following administration of intracavernosal vasoactive drugs unless contraindicated (e.g. in sickle cell disease).

Penile trauma

Penile trauma is rare; when it does occur it is most commonly experienced during intercourse or masturbation or by falling on the erect penis. Unilateral rupture of the tunica albuginea is usually the result of trauma and if not surgically repaired, deformity and erectile dysfunction may occur. The diagnosis of rupture of the tunica is made when there is disruption seen in the tunica albuginea (Figure 21.5).

Localization of the penile fracture (Figures 21.6, 21.7) is useful to the surgeon, allowing smaller localized incisions to repair the fracture, rather than extensive degloving.
Neurophysiologic testing in erectile dysfunction

Yoram Vardi and Ilan Gruenwald

Introduction

Erectile dysfunction (ED) in patients with neurological disorders that affect the central nervous system (CNS) or peripheral nervous system (PNS) is often suspected to be neurogenic. Whilst medical history and clinical examination provide the basis for diagnosis of neurogenicity of ED, a large variety of tests are available to the clinician for further evaluation. Tests can be classified into those detecting somatic motor pathways, sensory pathways, reflexes, and autonomic responses. However, despite the variety of tests, diagnosis of neurogenic etiology for sexual dysfunction in clinical practice is not a simple task.

A major difficulty in the use of neuropsychological tests to diagnose the neurogenic etiology of ED is the lack of a ‘gold standard’ test by which neurogenic ED is defined and to which all tests can be compared. As the search for such a test continues, one has to accept the imprecision of this diagnosis and the difficulties in assessing the usefulness of the various neuropsychological tests discussed later in this chapter.

The neurological examination

Discussion of the full neurological examination is beyond the scope of this chapter, and therefore a brief description is given for a short assessment of the neural function of the sacral region, consisting of motor, sensory, and reflex examinations.

Motor examination

The motor examination should consist of the following assessments and considerations.

- Plantar flexion of the foot and abduction of the thighs are L5–S1 innervated functions.
- Hyperextension of the thigh is done by the gluteus maximus, via roots S1 and S2.
- Power of the anal sphincter, an S2–S4-innervated muscle, is tested by rectal examination.
- Muscle tone is assessed by asking the patient to relax his lower limbs and then to flex and extend them several times. Increased tone is an expression of a central motor lesion, spasticity is typical of pyramidal lesion (e.g. after a stroke or in multiple sclerosis), and rigidity occurs in extrapyramidal disorders (e.g. Parkinson’s disease).

Sensory examination

The sacral-innervated area includes the buttocks, the perineum, the penis, the scrotum, the posterior parts of the thighs, and the plantar and lateral dorsal parts of the foot. Sensory examination should identify the presence of sensory loss. Further, sensory examination can distinguish disorders of large nerve fibers from disorders of small nerve fibers. Large fibers affect the sensations of touch, vibration, and joint position. Touch can be examined using cotton or a finger, and vibration can be tested by using a 128 Hz vibrating fork. A disorder of the small fibers affects the sensations of temperature and pain. Thermal sensation is examined by using water tubes containing warm and cold water (the patient being asked to identify the sensation evoked by the tube). For pain, a pin is the easiest method (the patient being asked to verify the sharpness and painfulness of the sensation evoked).

Reflexes

The major sacral reflex is at the Achilles tendon. The most important surface reflex is the Babinski response. A positive Babinski response is a strong indication of a central lesion to the motor tract, at some level along the upper motor neuron. Another superficial reflex of possible relevance is the cremasteric reflex, an L1 level reflex elicited by tactile stimulation along the inner thigh. These reflexes disappear both in lesions of the CNS and in lesions of the PNS.

The bulbocavernosus reflex can be elicited at the bedside by performing a rectal examination with one hand and squeezing the glans penis with the other. A contraction of the anal sphincter should be felt by the examiner.

Clinical relevance

Data gathered from the neurological examination should help in establishing neurological abnormality, and in distinguishing between lesions of the CNS and the PNS. Detailed features are summarized in Table 22.1. Having completed the clinical examination, one gets a more precise idea of the type of neural injury the patient is suspected to have, and the appropriate
tests can be selected to supplement and establish further the correct diagnosis.

Neurophysiological tests

Tests of the motor system
Electromyography
A comprehensive description of electromyography (EMG) is beyond the scope of this chapter. Briefly, the electrodiagnostic test has two subtests—nerve conduction study (NCS) and needle electromyography (EMG) both reflect activity in large myelinated somatic fibers.

Procedure Needle electromyography is performed by inserting a special needle into the skeletal muscle, and recording activity in several situations. First, a recording is made in resting muscle, which should be electrically silent. In the case of an axonal lesion to the innervation of the recorded muscle, abnormal spontaneous activity starts 1–2 weeks after injury and usually abates 3–4 months later.

Then, a recording is made under conditions of mild activation of the muscle, in which case individual motor units can be seen. The shape of the motor units changes after injury to the innervation of the recorded muscle—units grow larger and longer and have many polyphasic potentials. This occurs roughly 1 month after denervation, and remains present for many years.

Finally, a recording is made under conditions of full power recruitment—the subject is requested to contract the muscle fully while the recording is being taken. A reduced recruitment pattern is seen in denervation.

In the context of ED, the skeletal muscles of relevance are the bulbocavernosus muscle and the anal sphincter.

Normal findings In the normal pelvic floor, no activity is seen at rest, units are of less than 10 ms duration, and recruitment is full.

Clinical role Diseases that affect the continuity of the pudendal nerves can be diagnosed with this technique. Lumbar disc disorders, pelvic anatomical lesions, and pelvic surgery can damage both somatic pudendal and autonomic hypogastric and pelvic nerves (or their roots) and be diagnosed by pelvic floor EMG.

Magnetic stimulation
Application of a magnetic field over the scalp above the motor cortex induces an electrical field and activation of the corticospinal (pyramidal) tract. Activation can also be achieved by magnetic stimulation over the relevant spinal roots. It should be noted that the pyramidal fibers and their subsequent alpha-motor neurons are large and fast myelinated fibers. Response can be recorded from activated striated muscle by surface or needle electrodes.

Procedure A magnetic coil is positioned above the scalp or spine, and discharged. The procedure is painless. The recorded response can be facilitated if the subject is asked to partially contract the recorded muscle during stimulation. Central conduction time is calculated by subtracting the latency between the nerve root and the muscle from the latency between the cortex and the same muscle.

Normal findings A study by Opsomer et al. recorded a cortex–bulbocavernosus muscle latency of 28.8 ms during rest and 22.5 ms during contraction in 18 healthy male volunteer subjects. Central conduction times for the bulbocavernosus muscle were 22.4 ms at rest and 15.1 ms with facilitation. In a study by Dressler et al., a central motor conduction time of 15.7 ms was reported in six normal males.

Clinical role In a small number of patients with neurogenic ED, abnormalities of conduction have been reported.

Tests of sensory system
Penile biothesiometry
Biothesiometry is a cost-effective sensory screening test that measures the vibration perception threshold of the skin. This procedure is performed using a portable hand-held electromagnetic vibration placed through a flat round probe. Vibration amplitude is controlled by the examiner, and is said to be linearly related to the applied voltage, which can range from 0 V to 50 V.

Procedure This test is performed by application of the vibrating head perpendicular to the skin. Stimulus intensity is gradually increased from zero until vibration is felt by the subject; the amplitude at this level is measured and recorded as the vibration perception threshold. Usually three or more readings are taken, and the mean is regarded as the resulting threshold. In addition to the appearance threshold, one could

<table>
<thead>
<tr>
<th>Table 22.1 Features that characterize central and peripheral lesions according to physical examination</th>
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<tbody>
<tr>
<td><strong>Central nervous system lesions</strong></td>
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<tr>
<td>Hyperactive tendon reflexes</td>
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<tr>
<td>High muscle tone of the spastic or rigid type</td>
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<tr>
<td>Positive Babinski’s sign</td>
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<tr>
<td>Lack of significant muscle atrophy</td>
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<tr>
<td>Sensory loss in a hemi-body distribution or in the lower limbs</td>
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also measure the disappearance threshold. The stimulation site can be anywhere on the body surface. Routinely, tests are performed either on distal extremities or, in the urological context, on the penis, either at the shaft or the glans.

### Normal findings
Two studies are available that provide normative data for penile biothesiometry. One by Padma-Nathan (Study I in Table 22.2) looked at 118 potent males, yielding an age stratified nomogram. A second by Breda et al. (Study II in Table 22.2) studied 350 men across all age groups. Age dependency is noted, which can be explained by skin atrophy or by progressive loss of peripheral neurons with increasing age.

### Clinical value
Two studies have attempted to evaluate the role of biothesiometry in the evaluation of ED. Padma-Nathan tested biothesiometry against penile evoked potentials. In a group of 137 men with ED, 38 had normal vibratory thresholds, 80% of which had normal evoked potentials. This figure increased to 93% in patients less than 60 years old. Of the 99 patients with an abnormal threshold, only 47% had abnormal evoked potentials. The author concluded that penile biothesiometry is far more sensitive than evoked potentials, making it an excellent screening tool for sensory deficit in ED. Bemelmans et al. studied 31 men with ED, testing biothesiometry against penile and foot evoked potentials and bulbocavernous reflexes. They looked for a correlation between results, but found none. The authors concluded that biothesiometric investigation of penile glans innervation is unsuitable for the evaluation of penile innervation and cannot replace neurophysiological investigation. These studies obviously cannot provide a clear conclusion regarding the role of biothesiometry in ED evaluation, but this simple cost-effective screening tool can be useful in selecting patients for more sophisticated neurophysiological evaluation.

### Thermal testing
Thermal testing is a psychophysical test, in which an objective stimulus – a controlled quantitated temperature surge – is given, whereas the response is subjective. The thermal sensations and pain are somatic, but they are conveyed by small nerve fibers and therefore abnormal findings might be an indirect reflection of an autonomic neuropathy.

### Procedure
Thresholds for these sensations are obtained by attaching to the skin a thermode that is capable of changing its temperature in a controlled manner. The subject is requested to comment on the perceived sensations in response to series of thermal stimuli.

### Normals findings
Normative data for penile thermal sensations were given by Yarnitsky et al. In a group of 25 normal volunteers, 95% upper limit values obtained through the method of limits were 27.1°C for cold sensation and 35.6°C for warm sensation, using an adapted temperature of 32°C and a rate of temperature change of 1°C per second (Table 22.3).

### Clinical role
Bleustein et al. found that, in a group of 107 patients, warm thermal threshold measurements (taken at the glans penis) can be used to assess the neurological status of the penis, thus offering a quick, non-invasive, accurate method of evaluating penile neuropathy in an office setting.

### Dorsal nerve conduction
Dorsal nerve conduction measures the conduction velocity along the dorsal penile sensory nerve (a pudendal branch) by applying electrical stimulation at one end and recording the evoked potential (EPH) at the other. Conduction studies as a rule, sample the fastest, myelinated fibers.

### Procedure
Indirect measurement of conduction velocity was described by Gerstenberg and Bradley, who performed bulbocavernous reflex latency measurement using stimulation at two sites – the distal end and the proximal end of the penis. Latency difference was used to calculate dorsal nerve
Conduction velocity. In 1984, Bradley et al. directly measured the conduction velocity of the dorsal nerve using the following technique. The penis is gently stretched and two stimulating electrodes 0.5 cm in diameter are pasted on the dorsal of the glans 1–2 cm apart. Two disk recording electrodes are placed on the dorsum of the penile shaft near the symphysis pubis. A square wave stimulus with a duration of 0.1 ms and a frequency of 1.7 Hz is delivered, and the action potential is recorded. Distance is divided by latency to calculate conduction velocity. Several technical modifications of this test have been suggested.

Normal findings Bradley et al. found a mean normal velocity of $27.4 \pm 3.4$ m/s and a mean amplitude of $12 \pm 6.1$ µV. When a 1-pound (454 g) weight was added (thus stretching the penile shaft), the velocity increased to $33 \pm 3.8$ m/s. When Clawson et al. used an alternative stretching device they noted a mean velocity of $36.2 \pm 3.2$ m/s and an amplitude of $2.29 + 1/08$ µV in 20 normal subjects.

Clinical role Gerstenberg and Bradley tested 14 diabetic patients with ED, using bulbocavernosus reflex latency calculations. Velocity for normal controls was $23.5$ m/s with a range of $21.4$ m/s to $29.1$ m/s, compared with diabetics whose mean conduction velocity was $10.9$ m/s. Lin and Bradley measured slower velocity in the dorsal nerve in 20 insulin-dependent diabetic patients with ED than in normal controls. In both studies, no comparison was made with diabetic potent patients. Kaneko and Bradley found that the average conduction velocity in diabetic patients with ED was $37$ m/s compared with $45$ m/s in non-diabetic patients.

Nerve conduction of the dorsal nerve of the penis can be valuable in the evaluation of peripheral sensory nerve function, especially in patients with diabetes. However, the sensitivity and specificity of this test have not been evaluated, and technical questions are still unanswered. Consequently, the role of this test in the evaluation of ED is limited.

Somatosensory evoked potential studies

Somatosensory evoked potential (SEP) studies are based on the application of an external stimulus to sensory receptors and the recording of the scalp response time. As scalp responses have low amplitude, averaging is usually required. Most SEP studies utilize large nerve fibers in the PNS, and dorsal columns in the CNS en route to the primary somatosensory cortex. In the context of ED, several strategies have been utilized for SEP studies: stimuli have been applied to the dorsal penile nerve, the vesicourethral junction, and the lower limb nerves.

Procedure Electrical stimuli of non-painful intensity are repeatedly given to the stimulation site. Usually several hundreds are required in order to record a clear response. Electroencephalogram electrodes are mounted on scalp sites appropriate for somatosensory recordings. Recording can also be obtained from the spinal cord. Specific machinery is required for amplification, filtration, and averaging of the recorded signals.

Normal findings Opsomer et al. described normal values in 18 subjects, finding response over the scalp at a maximal latency of $44.2$ ms. Mean central conduction time was $27$ ms (range $23.5–30.4$ ms). Ertekin et al. found a mean peak of the scalp wave at $43$ ms in 14 normal subjects.

Clinical role Ertekin et al. found prolonged SEP latency in ED patients with CNS disorders – in 55% of multiple sclerosis patients with ED, in 33% of patients with spinal cord lesions and in 17% of patients with Parkinson’s disease; and normal latency for patients with psychogenic ED and diabetic patients with ED. Pickard et al. found prolongation of the SEP latency in neurogenic ED, but noted that the results could be predicted by history and physical examination, leaving little clinical value for the test. Spudis et al. evaluated the amplitude of the negative wave of the SEP. They studied 128 unclassified ED patients, searching for a detector of neurogenic etiology; 16.4% of the patients had abnormal findings, and the authors suggested that SEP could be used as a screening tool for neurogenic ED. Tackmann et al. studied 246 patients, in 63 of whom a pathological response was found.

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<th>Table 22.3 Normal values for penile thermal testing</th>
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<tr>
<td><strong>Method, modality</strong></td>
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<tr>
<td>Limits, cold sensation</td>
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<tr>
<td>Limits, warm sensation</td>
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<tr>
<td>Levels, cold sensation</td>
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<td>Levels, warm sensation</td>
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*Although the 95% confidence limit is calculated based on two-tailed values, only the upper limits (beyond which subjects are considered abnormally hyposensitive) are shown. Data from J Urol 1996; 156: 391–3.*
Testing of the reflexes

Bulbocavernous reflex

Measurement of the bulbocavernous reflex has been commonly used in the evaluation of underlying neurological disorders in erectile and lower urinary tract dysfunctions. This test was first described by Rushworth and introduced into clinical routine by Ertekin and Reel. The bulbocavernous reflex attempts to determine the integrity of the neural reflex arch of the sacral cord, S2–S4. The afferent arm of the reflex consists of the pudendal nerve and its distal sensory branch, the dorsal penile nerve. Efferently, it is the pudendal nerve that serves the reflex. A prolonged bulbocavernous reflex latency or the absence of a reflex is considered a sign of neurological dysfunction.

Procedure Stimulating surface electrodes are placed on the penis and a concentric needle electrode is inserted in the bulbocavernous muscle either on one side or on the midline. Localization of the needle is verified by observing the electrical response to a manually elicited reflex, as well as through asking the patient to contract and relax his pelvic floor muscles. Stimulation is administered through electrodes placed on the penile shaft using rectangular stimuli of 0.1–0.5 ms at random intervals. Bulbocavernous reflex response and latency time are monitored and recorded by an EMG amplifier. A major technical point is relaxation of the muscle by the patient. Barron et al. suggested surface recording of the reflex, by placing the electrode over the perineal musculature.

Aside from this technique, several similar techniques have been described with different stimulation and recording sites: stimulus can be applied at the vesicourethral junction, perineum, or at the anal sphincter.

Normal findings Tackmann et al. studied 39 potent males, finding a mean bulbocavernous reflex latency of 34.6 ms (95th percentile 43.9 ms, 99th percentile 44.9 ms). Sarica and Karacan found a latency of 33.3 ± 3.7 ms in 14 normal controls. Bemelmans et al. found a range of 20–40 ms in 50 healthy volunteers. Ertekin and Reel found a range of 27.5–42.5 ms in 14 normals subjects.

Clinical role In the pioneering paper by Ertekin and Reel, a substantial prolongation of reflex latency was found in cases of ED caused by cauda equina lesions, and, to a lesser degree, in polyneuropathies. A normal response was found for patients with spinal cord disease and functional ED. Later studies can be found that advocate routine use of this test because of the high rate of abnormality, as well as studies criticizing its indiscriminate use because of the low rate of abnormality, at least in some etiological groups. Tackmann et al. found pathological results in 125 of 252 patients with ED of various etiologies: 5 out of 7 with multiple sclerosis, 26 out of 46 with polyneuropathies, 16 out of 23 with trauma, and 78 out of 176 patients with ED but no neurological disorder. Bemelmans et al. studied 126 patients with ED of various etiologies, finding pathology in 21%. Lavoisier et al., on the other hand, found 19 pathological results in a group of 90 ED patients. However, 8 of these had normal nocturnal penile tumescence, so calling into question the specificity of this test in the evaluation of ED.

Specifically in diabetic patients, Parys et al. found pathological results in 21% of patients with ED. Desai et al. raised the question of the role of sacral response studies in diabetic ED, suggesting a low yield of the tests. Similarly, Vardi et al. found pathological bulbocavernous reflex responses in only 4.5% of 45 diabetic ED patients.

The authors of this chapter suggest a problem-oriented approach in the use of the bulbocavernous reflex. The test is most relevant for patients with lesions in the lower spinal cord (cauda and pelvis). Pathology to the roots or pudendal nerves is likely to result in a prolonged or absent response. The use of the bulbocavernous reflex in patients with polyneuropathy (including those with diabetes) and in patients with no suspicion of a neurogenic cause for their ED is discouraged.

Testing of the autonomic nervous system

Sympathetic skin response

A systemic sympathetic activity can be evoked by various maneuvers such as a painful stimulus, a deep breath, or mental effort. The response is believed to reflect sudomotor activity, which is mediated by cholinergic sympathetic fibers. This is an objective neurophysiological measure of autonomic activity, and hence it is attractive for detection of autonomic dysfunction as a cause of ED and ejaculatory problems.

Procedure A skin response can be picked by mounting two electrodes on the penis as well as on the hand or the foot. Usually an electrical stimulus is used, owing to convenience of recording. One of the major limb nerves is stimulated electrically, and a recording window of at least 2 seconds’ duration is opened.

Normal findings Derouet et al. studied 20 normal volunteers. The median nerve at the wrist was stimulated, with recordings from both the penis and the leg. Penile response was recorded in 80% of subjects, and the mean latency was 1.4 seconds, while mean latency to leg was 1.3 seconds. Ertekin et al. studied the amplitude in 14 normal subjects of the sympathetic skin response, finding an amplitude of 1.1 ± 0.9mV in the flaccid state and 0.55 ± 0.6mV during papaverine-induced erection.

Clinical role Derouet et al. found prolonged latency of the sympathetic skin response in 12 out of 46 patients, some of which could have neurogenic ED (e.g. resulting from diabetes or vincristine). Zgur et al. found a 53% diminution of the amplitude of the sympathetic skin response measured on the limbs of 30 diabetic patients. Dettmers et al., also measuring on the limb, found the sympathetic skin response to be the least sensitive test in diagnosing neurogenic ED when compared with the bulbocavernous reflex and pudendal
somatosensory evoked potentials.\textsuperscript{31} Data are very limited regarding the clinical use of this test. At the present time no firm conclusion can be drawn.

Corpus cavernosum electromyography

In the absence of any definitive test for the diagnosis of neurogenic ED, efforts have been made over the past decade to record electrical activity from the smooth muscle in the corpora cavernosa. If successful, this method is expected to give a direct definitive diagnosis of neurogenic ED.

Procedure Recording can be made either by a surface electrode over the penile shaft or by a needle electrode inserted into the corporal tissue. Long recording sessions (typically at least 30 minutes) are required, and the equipment should be able to work at a very low band pass, since the routine filter setting is 0.1–30 Hz.\textsuperscript{12} Jiang et al. have suggested using corpus cavernosum EMG during morning naps and have been able to show that this methodology is feasible and valid.\textsuperscript{34} They demonstrated that corpus cavernosum potentials consistently disappeared during tumescence and erection, while continuous oscillations in the potential reappeared during detumescence.\textsuperscript{33}

Normal findings Stief et al. described normal potentials (surface-recorded), with 8–18 second duration and an amplitude between 250 µV and 750 µV, with between eight and 22 phases.\textsuperscript{14} These authors and others\textsuperscript{35–37} give importance to the synchrony of activity between the two corpora; in normal subjects nearly full synchrony is expected. Yarnitsky et al. found that some of the activity in the corpora is simultaneous with limb activity in response to sympathetic activating maneuvers (see above) and therefore some of the corporal activity is part of a generalized sympathetic response, and only the rest is specific penile activity.\textsuperscript{38}

Clinical role Abnormal potentials, with loss of synchrony between the two corpora, is seen in many ED patients (51.6% of 214 patients in Stief’s study).\textsuperscript{34} Wagner et al. found desynchronization between the two corpora in 6 out of 10 diabetic patients with ED and in 18 out of 23 patients after radical cystectomy.\textsuperscript{35} These results are controversial in the experience of the present authors\textsuperscript{39} and of others.\textsuperscript{40} Recently, Jiang et al. made an effort to standardize the recording methodology (using multichannel monopolar recording), to control the measurement conditions, and to define exactly the parameters that are used to characterize corpus cavernosum potentials.\textsuperscript{36} Meulaman et al., using the same methodology, have been able to discriminate between ED patients with conditions that are associated with cavernous smooth muscle degeneration or autonomic neuropathy, and men with normal erectile function.\textsuperscript{37}

Despite the fact that corpus cavernosum EMG may be able to give a direct measure for neurogenic ED, it has never reached clinical application owing to a lack of standard equipment and standard recording techniques, a lack of consensus on the measurable parameters, and a lack of objective criteria to characterize the recorded signals. Until clearer basic work, normative data, and solid clinical data are available, this method cannot be recommended for clinical use.

Figure 22.1 Characteristics of each neurophysiological test and the relative anatomical neural pathways that they investigate. Arrows indicate tests when a stimulus–response relationship is studied, loops represent reflexes, and blank lines represent tests that sample ongoing activity. Large and small relate to fiber size in the peripheral nervous system. EMG, electromyography; MAG, magnetic stimulation; DNV, dorsal nerve velocity; SEP, somatosensory evoked potentials; BIO, biothesiometry; TT, thermal testing; BCR, bulbocavernous reflex; CC/EMG, corpus cavernosum EMG; SSR, sympathetic skin response.
Conclusion

The neurophysiological evaluation of the patient with ED should be specifically tailored for the individual patient – no ‘automatic’ routine work-up can be prescribed. We suggest its use in several groups of patients, divided mostly by history (Figure 22.1).

- Patients suspected of having CNS lesions, such as multiple sclerosis and Parkinson’s disease. For these patients, as can be seen in Figure 22.1, magnetic stimulation and SEP studies are the most relevant tests, evaluating motor and sensory function, respectively.

- Patients with a history compatible with polyneuropathy, such as in diabetes or renal failure, after chemotherapy, and with hereditary neuropathies. In such cases the focus of evaluation is in the peripheral system – nerve conduction studies, EMG, and thermal testing in the lower limbs are the most relevant tests.

- Patients with a history suggestive of a low spine or pelvic disorder interfering with penile innervation, such as herniated lumbar disc, pelvic fracture, and radical prostatectomy. EMG of the sphincter muscles, bulbocavernous reflex testing, dorsal nerve conduction studies, and magnetic stimulation of the genitalia are recommended.

REFERENCES


Biopsy of the corpus cavernosum
Eric Wespes

Introduction
The cavernous sinusoids, consisting of bundles of smooth muscle, elastic fibers, and collagen, represent the key to the problem of erectile dysfunction (ED); demonstration of alterations in them could eventually spare patients from reconstructive surgical treatment. Electron microscopic studies have demonstrated modification of the smooth muscle cells in patients with vascular impotence. However, the tissues examined were obtained during surgery, when the therapeutic procedure was already being performed.

Vasculogenic impotence represents the most important etiology in organic ED. Several different techniques have been developed to diagnose arterial or venous insufficiency. Duplex sonography in conjunction with intracavernous injection of vasoactive drugs is the gold standard method for providing information about arterial blood flow into the penis. Pharmacocavernometry and cavernography appear to be able to determine the venous hemodynamic status of the corporal bodies. Use of the Biopty gun to perform penile biopsy under local anesthesia appears to be a simple and reliable method to obtain sufficient tissue for histologic analysis.

Description of the biopsy method
First approximately 1 ml lidocaine is infiltrated into the skin of the penis. The puncture is performed in the balanopreputial groove on the dorsolateral side. The biopsy needle is introduced longitudinally through the tunica albuginea into the corpus cavernosum. With one hand, the penis is kept slightly stretched and, with the other hand, the needle is fired from an anterior to a posterior trajectory. The needle is then removed and the tissue fragments are placed in Bouin’s solution.

In all the patients, adequate tissue was obtained for histological analysis. Corpus cavernosum tissue can be easily identified with the intracavernous smooth muscle fibers and collagen. None of the outpatients experienced significant pain at biopsy or required any postoperative analgesia. No lesions were observed with the Doppler analysis of the cavernous arteries. Cavernometry readings were similar after the biopsy to what they were before.

Discussion
The Biopty gun procedure is cost effective and can be performed in the office under local anesthesia. The total procedure usually lasts less than 10 minutes. The place of this method in the assessment of patients with ED and a definition of the histological criteria by light or electron microscopic studies must be determined to include or exclude patients for penile surgery.

When this new simple technique for obtaining cavernous tissue was first described, it was considered to be very aggressive. It is clear that it is an invasive technique that does not yet have a place in the investigation or the treatment of patients with ED. However, it has been used by other well-known teams to study the pathophysiology of impotence or other penile pathologies, such as Peyronie’s disease.

Advances in impotence research and increased knowledge of the pathophysiology of ED have demonstrated that the erectile response decreases with age. Elderly men take longer to obtain an erection and find it more difficult to sustain one. The prevalence of ED ranges from 52% in men aged 40–70 years to > 95% in men older than 70. Relaxation of the intracavernous smooth muscles is the key factor in the mechanism of penile erection. We have demonstrated that the percentage of penile muscular cells decreases with aging; it is 46% in men younger than 40 years, 40% in men between 41 and 60 years, and 35% for men older than 60 years. This decrease in smooth muscle content may be responsible for the decline in erection in older men.

This reduction occurred throughout both cavernous bodies. Vascular impotence is a diffuse penile disease; therefore, a cavernous body biopsy can be used to study the penile structure in the assessment of vascular impotence.

In patients with organic ED, a decrease in smooth muscle cells was observed and the decrease is more important in patients with arterial disease. Objectively, the percentages of elastic fibers in corpus cavernosum tissues in potent and impotent men have been measured. The mean percentage
of elastic fibers was 9% in normal patients. In patients with venous leakage, a significant decrease in the amount of elastic fibers of 5.1% was observed. In patients with arterial disease, the decrease was 4.3%. No correlation was observed between the reduction of the elastic fiber quantification and age. Change in elastic fiber content may alter the relaxation properties of cavernosal tissue and play a role in the development of ED.\(^1\)

The role of the different components of the corpus cavernosum is very important in the physiopathology of ED. The precise function of collagen fibers in erectile physiology is controversial. My team measured the different types of collagen (I, III, IV) in the corpus cavernosum of impotent and potent men using cell image analysis and immunohistochemistry. We found differences in the distribution of collagen I, III, and IV in each pathological group (arterial ED, cavernous ED, and psychogenic ED). The augmentation of collagen I and the light diminution in collagen III make the corpus cavernosum less compliant, which is traduced clinically by an alteration in the filling of the vascular spaces and by dysfunction of the veno-occlusive mechanism. The diminution in collagen IV shows an alteration in the function of endothelial cells. That we found a diminution in collagen IV content in the psychogenic group makes us infer that psychogenic impotence could be the first stage of organic impotence.\(^2\)

Objective quantification showed no difference in the numbers of cavernous endothelial cells between potent and impotent men, which is surprising considering that the other penile structures (smooth muscle cells, collagen fibers, and elastic fibers) demonstrate modification in impotent patients. However, the function of the endothelial cells could be perturbed and be the origin of ED.\(^3\)

Study of the intracavernous structures allows us to appreciate the therapeutic effects of oral drugs, intracavernous injections, or surgery. To better select responders and non-responders to sildenafil, a hemodynamic and morphometric study in non-responders was conducted. Severe vascular lesions and atrophy of the smooth muscle cells are observed mainly in non-responders. Age, diabetes, and hypogonadism seem not to be related to the failures. Poor responses to intracavernous injections could be used as a predicting test for sildenafil users. Apomorphine should not be given to the non-responders.\(^4\)

In patients treated with intracavernous prostaglandin E-1 injections, this drug does not seem to influence growth factor in vivo as it has been demonstrated in vitro,\(^5\) and therefore it does not decrease the percentage of collagen tissue that could be used for remodeling penile smooth musculature.\(^6\) In patients operated on for venous ligation, the best results are obtained in those with sufficient smooth muscle content.\(^7\)

Penile biopsies performed 2 and 12 months after radical prostatectomy have shown a progressive increase in penile organized collagen content and a decrease in smooth muscle cells and elastic fibers.\(^8\)

Early use of high doses of sildenafil after radical prostatectomy could preserve smooth muscle content. Percutaneous biopsies both during surgery and 6 months after surgery under local anesthesia have demonstrated preservation of the percentage of smooth muscle cells in patients treated with daily use of sildenafil 50 mg or 100 mg.\(^9\)

In aged rats, fibrosis of the cavernous tissue is observed. Exploring the pathogenesis of this phenomenon in rats, the first important finding is that tumor growth factor (TGF) beta-1 is higher in penile tissue of old rats than in the penile tissue of young rats.\(^10\) Under normal conditions, TGF-beta-1 maintains cell numbers by directly inhibiting cell proliferation and by controlling the potent mitogenic actions of platelet-derived growth factor (PDGF), a companion cytokine. TGF-beta-1 also regulates the amount of extracellular matrix (ECM) by balancing new synthesis and deposition of ECM by degradation and removal with proteases. Under ischemic conditions, TGF-beta-1 induces its own mRNA, leading to a further increase in TGF-beta-1 synthesis, which reinforces the development of severe fibrosis. TGF-beta-1 gene expression is significantly increased in the penile tissue of older rats compared with young rats. Hypoxia has been demonstrated to induce the expression of TGF-beta-1 in several tissues; therefore, penile ischemia may cause increased TGF-beta-1 expression, leading to ECM deposition and, eventually, penile fibrosis.

A correlation between oxygen tension in the human penis has been demonstrated with the percentage of smooth muscle fibers.\(^11\) Therefore, the number of muscular fibers depends on good oxygenation of the penis; otherwise, ischemia induces fibrosis by stimulating TGF-beta-1. It seems that the histological alterations start distally, in the very small penile arteries.\(^12\)

Apoptosis is another phenomenon that occurs after neural lesions, mainly in patients operated on for radical prostatectomy. Bilateral cavernous neurotomy induced significant apoptosis of smooth muscle cells on postoperative day 2 in rats, particularly in the subcutaneous area, causing veno-occlusive dysfunction; however, the endothelial cells did not demonstrate any apoptotic mechanism.\(^13\) The difference between smooth muscle fibers, in which degeneration occurred, and the endothelial cells, in which there were no alterations, could explain why the benefit induced by a reliability phosphodiesterase type 5 inhibitor approach compared with on demand or every day or every other day does not make any difference.\(^14\) The endothelial cells and their production of neurotransmitters are not perturbed.

### Conclusion

Penile biopsy is certainly a method that can allow the study of the intracavernous structures. What its place will be in the assessment of patients with erectile dysfunction remains to be determined. At the present time, it is certainly not recommended by any guidelines. However, in the future, with new therapeutic approaches such as gene therapy, it could be integrated into the therapeutic arsenal for the treatment of patients with ED.
REFERENCES

Endocrine evaluation of male sexual function

Sanjay N Mediwala and Glenn R Cunningham

Introduction

The endocrine evaluation of male sexual function centers primarily on the history and the physical and laboratory evaluation of three endocrine conditions: hypogonadism, hyperthyroidism, and diabetes (with associated neuropathy and vasculopathy). Diagnosis of hypogonadism leads to its own differential diagnosis: testicular failure versus central hypogonadism.

Hypogonadism

Hypogonadism is defined as a clinical syndrome that results from failure of the testes to produce physiological levels of testosterone (androgen deficiency) and the normal number of spermatozoa (due to disruption of one or more levels of the hypothalamic–pituitary–gonadal axis). Low testosterone levels are observed in 2–21% of men presenting to a physician with erectile dysfunction (ED).

Most of the variation probably is due to differences in patient populations. Diagnosis of hypogonadism is important because it may provide clues to underlying illnesses such as hypothalamic, pituitary or testicular disease, hemochromatosis, or obstructive sleep apnea.

Further, hypogonadism itself has been associated with reduced life expectancy, increased risk of having or of developing the metabolic syndrome, development of type 2 diabetes, increased visceral fat, and increased risk of coronary heart disease.

The management of hypogonadism with these conditions in older men is more controversial. Once diagnosed, however, hormonal therapy is an option that has been demonstrated to improve many domains of sexual function.

Clinical history

Research continues to clarify the role of androgens in male sexuality. Sexual desire, the production of seminal fluid, and penile tumescence are responsive to androgen. The clinical history, however, may only provide general clues as to the diagnosis of hypogonadism, and can be quite variable. The clinical presentation varies on the basis of the severity and length of androgen deficiency, age, associated illnesses, and androgen sensitivity.

A history of non-completion of puberty provides immediate concern for the possibility of longstanding hypogonadism, whilst a history of reduced libido and spontaneous erections are suggestive of hypogonadism in the patient who has completed development normally. The quality of morning erections correlates with nocturnal penile tumescence. Breast discomfort may be an early symptom of gynecomastia. Hair pattern – specifically, loss of body, axillary and pubic hair and a noticeable reduction in shaving – can be suggestive of hypogonadism, as can reduced muscle mass and strength. Hot flushes are suggestive of primary hypogonadism, but can be caused by central hypogonadism.

Psychiatric symptoms, including lack of energy, irritability, sad moods, decreased enjoyment of life and decreased sense of well-being, have been mentioned in reviews of hypogonadal men. These symptoms may be present in a subset of the hypogonadal population, though pervasive symptoms linked solely to hypogonadism are unlikely.

In a short-term study of induced hypogonadism in young, otherwise healthy men without prior psychiatric history, 1 month of testosterone suppression led to symptoms of depression in 3 of 31 men. The feeling of being emotionally charged decreased with induced hypogonadism. The subjects’ daily rating of sadness, anxiety, irritability, mood lability, and anhedonia did not change during the time of hypogonadism, nor did measurements of mood stability, social avoidance, work productivity, aggression, or impulsivity.

Studies of elderly hypogonadal men have been conflicting and their interpretation limited by lack of controls. Most indicate that some patients exhibit depressed mood, but severe depression is rarely, if ever, caused by testosterone deficiency.

Several questionnaires have been used to screen for hypogonadism. Unfortunately, each lacks specificity and some lack sensitivity. Most experts think that they are not helpful.

Physical examination

The physical examination for endocrine causes of hypogonadism focuses on the physical signs of completed puberty and evidence for acquired post-pubertal androgen deficiency. Body hair pattern should be examined. The appearance of a female escutcheon (triangular escutcheon) and lack of androgen-dependent hair on the chin, cheeks, upper lip, inner thighs, and lower back are suggestive of longstanding hypogonadism. Gynecomastia (concentric breast tissue that is palpable as a discrete subareolar plaque) results from the
relative increased ratio of estradiol to testosterone (from peripheral conversion of testosterone to estradiol). When there is concern that the individual may have longstanding hypogonadism (extending from puberty), body proportions should be measured. In normal development from childhood to adulthood, there is a progressive decrease in upper to lower body ratio from 1.7 at birth to 1.0 at normal cessation of growth. Delayed puberty results in delayed skeletal maturation and epiphyseal closure, and thus to an upper to lower body ratio of <1.0 and an arm span >6 cm more than height. The upper body length should be measured from the top of the pubic symphysis to the crown of the head. The lower body length is the distance from the top of the pubic symphysis to the sole of the foot. Long slender hands (arachnodactyly) with long thin nail plates, similar to the findings in Marfan’s syndrome, may be present. Profound acquired hypogonadism is associated with accelerated bone turnover, and hypogonadism in the elderly may affect bone density by reducing both testosterone and estradiol levels. Osteopenia and vertebral compression may result in loss of height, though this may be unrecognized by the patient.

Examinations of the scrotal contents and the prostate are critical. A testicular volume <4 ml or length less than 2.5–3 cm in the longest dimension, is pre-pubertal in size. Males who have completed Tanner 5 development will typically have a testicular volume of >20 ml and a length >4.5 cm in the longest axis. Testes <4.0 cm are generally considered to be abnormal in adult men. Testosterone deficiency in younger men can cause regression of prostate size. However, the older man with benign prostatic hyperplasia may have an enlarged prostate that does not regress very much with androgen deficiency. It is important to exclude a prostate nodule or induration prior to treatment with testosterone, since clinical prostate cancers are usually androgen-responsive at the time of diagnosis.

Specific findings can assist in the diagnosis. Anosmia or midline defects can be associated with hypogonadotropic hypogonadism, including Kallman’s syndrome.

**Laboratory evaluation**

**Testosterone**

The diagnosis of hypogonadism rests on the symptoms and signs discussed above and on documentation of reproducibly low morning testosterone levels. The serum testosterone should be measured between 7.00 am and 10.00 am because diurnal variation occurs in younger and middle-aged men.

The choice of testosterone assay depends on the clinical scenario. Testosterone circulates in three fractions: free, tightly bound to sex hormone binding globulin (SHBG), and loosely bound to albumin. Only between 0.5% and 3% of testosterone is free. The free and albumin-bound fractions are considered bioavailable. The total testosterone and bioavailable testosterone fraction are proportional provided there are no alterations in SHBG. However, numerous conditions can result in elevated or decreased SHBG fractions (Table 24.1) and will alter the total testosterone measurement. These conditions may or may not affect the free or bioavailable levels. Thus, a patient can have a normal total testosterone level and a low free or bioavailable testosterone measurement or a low total and a normal free or bioavailable testosterone level.

Luteinizing hormone and follicle stimulating hormone

Once a low testosterone value has been established, measurement of serum gonadotropins will help to localize the cause of hypogonadism. Low testosterone results in decreased negative feedback to the hypothalamus and pituitary, leading to increased secretion of luteinizing hormone (LH) and follicular stimulating hormone (FSH). An (inappropriately) normal or frankly low serum LH and FSH in the setting of low testosterone is indicative of central hypogonadism. Elevated LH and FSH are appropriate pituitary responses, thus indicating testicular failure as the cause of low testosterone. Causes of testicular and central hypogonadism are listed in Table 24.2.

It should be noted that longitudinal studies have shown an age-related decline in serum levels of total, free, and bioavailable testosterone in healthy older men, an increase in SHBG with the decline in free and bioavailable testosterone occurring earlier. Usually this decline is associated with only small increases in FSH and LH until after the age of 70, and thus it has been attributed mostly to secondary (central) hypogonadism.

In cases of central hypogonadism, imaging of the pituitary should be considered – see below.

**Blood count**

Androgens stimulate erythropoiesis by increasing both renal production of erythropoietin and proliferation of erythroid

<table>
<thead>
<tr>
<th>Table 24.1 Conditions associated with altered SHBG</th>
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<tr>
<td><strong>Decreased SHBG</strong></td>
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<tr>
<td>Moderate obesity</td>
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<tr>
<td>Nephrotic syndrome</td>
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<tr>
<td>Hypothyroidism</td>
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<tr>
<td>Use of glucocorticoids, progestins,</td>
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<td>and androgenic steroids</td>
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precursors. In the androgen-deficient male, the red blood cell concentration drops to the normal reference range for females, approximately a 10% drop. The anemia is normocytic, and may be reversed by testosterone replacement.

Prolactin
The patient with low testosterone and low or inappropriately normal LH should be screened for hyperprolactinemia. The prevalence of hyperprolactinemia in men with erectile dysfunction (ED) is estimated at 2.4–4%, and treatment may result in return of erectile function. Somewhat more controversial is the screening of patients with ED but normal testosterone values for hyperprolactinemia. Buvat showed that half of the 12 ED patients in his study with moderate hyperprolactinemia (i.e. prolactin levels >35 ng/dl) had normal testosterone values. The ED of most men with mild increases in serum prolactin is not improved by treatment aimed at lowering serum prolactin.

Hyperprolactinemia can cause hypogonadism by suppression of gonadotropin-releasing hormone from the hypothalamus. In addition, prolactin may interfere with the conversion of testosterone to dihydrotestosterone. Loss of libido is a prominent feature often reported in cases of hyperprolactinemia.

Since hyperprolactinemia can be caused by a variety of medications (Table 24.3), prolactin-secreting tumors, hyperthyroidism, hypothalamic lesions, renal insufficiency, cirrhosis, and chest wall lesions, further evaluation is usually indicated if the prolactin level is >35 ng/mL.

### Imaging
For those patients with central (hypogonadotropic) hypogonadism and for those with unexplained hyperprolactinemia (>35 ng/mL), imaging of the pituitary, typically with magnetic resonance imaging (MRI), can be used to identify structural abnormalities. The prevalence of imaging abnormalities has been shown to be inversely proportional to serum testosterone levels when levels are subnormal. In one study, the hypogonadotropic ED patients in the lowest quintile of testosterone values had a 21.2% prevalence of hypothalamic or pituitary imaging abnormalities. The overall rate of imaging abnormalities was 6.7%.

Generally accepted guidelines state that imaging of the pituitary is indicated in cases of more severe central hypogonadism (testosterone <150 ng/dl) or when there is suspicion of pituitary disease (such as in cases of panhypopituitarism, persistent hyperprolactinemia, or symptoms of tumor mass effect). MRI scans may be obtained for younger men who have testosterone levels <200 ng/dl.

### Hyperthyroidism
Hyperthyroidism, a condition of excessive thyroid hormone release, can have significant effects on erectile function. It has been proposed that hyperthyroidism increases aromatization of testosterone into estrogen. The increase in estrogen raises levels of SHBG. Although free testosterone levels are usually normal, the ratio of estrogen to free testosterone is altered, which may contribute to ED. It has also been postulated that the increase in adrenergic tone caused by hyperthyroidism may cause ED, either through effects on smooth muscle or via behavioral or psychiatric effects.

The most common symptoms of hyperthyroidism are hyperactivity, irritability, heat intolerance, palpitations, fatigue, and weight loss. Physical signs include tachycardia, tremor, goiter, warm skin, proximal muscle weakness, and eyelid retraction. Biochemical diagnosis is made through the identification of high levels of thyroid hormone (total or
free T4 or T3) with a low serum thyroid stimulating hormone level.

**Diabetes mellitus**

Erectile dysfunction is more prevalent in diabetic men than in non-diabetic men, with an estimated prevalence of between 20% and 71%. Neuropathy and vasculopathy are typically implicated as the cause. In addition, however, low testosterone and low SHBG appears to serve as a risk factor for the future development of diabetes, and the prevalence of low bioavailable and free testosterone is greater in type 2 diabetic men. Testosterone treatment may be beneficial in some of these men. Low testosterone levels may be a cause of failure to respond to a phosphodiesterase type 5 inhibitor (PDE5I). The topic of diabetes and ED is addressed in Chapter 59.

**Conclusion**

The endocrine evaluation of ED should begin with identification of the symptoms and signs of hypogonadism. The history should be focused on the identification of pubertal status, risk factors for hypogonadism, libido, and the presence of nocturnal or early morning erections. The physical examination should identify patterns of body hair, testicular size, gynaecomastia, and muscle strength.

Additional work-up includes routine chemistries and blood counts, early morning testosterone, lipid profile, fasting glucose, hemoglobin A1c, thyroid hormone assays, and electrocardiography.

The free or bioavailable testosterone should be measured when conditions exist that alter SHBG, and there should be at least two consistent values below the reference range with associated symptoms to make the diagnosis of hypogonadism. Once the diagnosis of hypogonadism is made, further evaluation with FSH and LH can localize the site of the endocrine dysfunction, whether it is central or testicular. In the presence of central hypogonadism, prolactin should be checked. Imaging is restricted to those cases with total testosterone <150 ng/dl, persistent hyperprolactinemia, or other findings suggestive of hypothalamic or pituitary lesions.

Once a diagnosis of hypogonadism is made, consideration should be given to assessment of the bone mineral density for osteoporosis.

**REFERENCES**

25 The biopsychosocial evaluation of erectile dysfunction

Stanley E Althof and Rachel Needle

Introduction

Erectile dysfunction (ED) is a complex amalgam of interrelated biological, psychological, and contextual variables that combine to produce a distressing symptom for the man and his partner. Historically, ED was conceptualized in binary terms—it was either psychogenic or organic. In the 1980s, when fewer treatment options were available, this paradigm simplified treatment planning. Psychogenic patients were referred for psychotherapy, patients deficient in testosterone received hormone replacement, and patients with other ‘organic’ conditions were referred for penile prostheses.

Over time a third category, mixed erectile disorder, evolved to account for those patients with both psychological and organic factors. Yet, the notion of ‘mixed’ conveys a static rather than interactive and changeable concept. Disease conditions often change, as do psychological issues.

These shortcomings led to the development of the present biopsychosocial model that captures the ever-changing influences of biology and psychological life. It is a dynamic and additive model. Regardless of the precipitating causes, over time, changes in both biological and psychosocial domains occur. This biopsychosocial model encompasses both the psychological life of the man; the impact that the dysfunction has upon the man and couple’s sexual life; and the fluctuating influence of medication, lifestyle, and disease. By incorporating these issues into a global assessment of sexual problems, one arrives at a more accurate and comprehensive understanding of what precipitates and maintains the ED.

Additionally, the biopsychosocial model enables stepwise treatment recommendations in both the psychological and biological domains. The model also explains the failure of treatments for biological problems that ignore relevant psychological contributions, and psychological treatments that disregard the biomedical factors.

Biomedically, ED may be a symptom and latent signal for cardiovascular disease, a complication of diabetes or hypertension, an unfortunate consequence of a radical prostatectomy, or an adverse side effect of medications, like beta-blockers. Psychologically, interpersonally, and contextually, ED may stem from excessive performance anxiety or distractibility, depression, a deteriorating interpersonal relationship, substance abuse, or stress from life events that threaten to overwhelm the psychological resiliency of the man.

In addition to the biopsychosocial model, another organizing principle of evaluation is the division of etiological variables into predisposing, precipitating, maintaining, and contextual factors. Predisposing factors may make a man susceptible to ED. These may include diabetes, hypertension, substance abuse, restrictive upbringing, disturbed family relationships, inadequate sexual information, and traumatic early sexual experiences. Precipitating factors are ones that trigger the onset of ED and include a new medication, surgery, psychological impact of an illness or its treatment, depression, anxiety, infidelity, and relationship distress. Maintaining factors, which reinforce the persistence of the symptom, include performance anxiety, guilt, psychiatric disorder, relationship discord, loss of attraction between partners, fear of intimacy, impaired self-image, restricted foreplay, sexual myths, and poor communication. Finally, contextual factors include the current stresses in the man’s or couple’s life (e.g., unemployment, problems with the children).

Using the biopsychosocial model, this chapter presents an organized, step-by-step guide to the comprehensive assessment of ED. It follows a logical progression, examining all relevant biomedical and psychological aspects that may account for the symptom of ED and other related sexual problems such as hypoactive sexual desire disorder (HSDD) and ejaculatory dysfunctions. Such an evaluation is a collaborative enterprise between the clinician and patient that offers the patient a fresh perspective on the problem. The clinical synthesis derived from this process serves as a pragmatic road map for treating all the biopsychosocial variables identified that precipitate or maintain the symptom of ED.

Finally, there are diagnostic scales that clinicians may utilize to supplement the sexual history. This chapter also briefly reviews these scales, specifically addressing how they may best be utilized in assessing ED.

Approach to the assessment

It is important that the patient and clinician are mutually involved in the assessment process. Taking a collaborative approach, the clinician collects the sexual, medical, and psychological information, which he or she synthesizes into a cohesive treatment plan. When questions are asked in a logical and empathetic manner, the patient often gains a fresh perspective on the multiple issues related to his sexual problem.
When a patient (and potentially his partner) begins assessment, they often characterize the ED in phrases such as, ‘My penis doesn’t get hard any more’. The patient usually has an unsophisticated view of his ED and the impact on his life. Often he is unaware of the relationship between his symptom and multiple disease processes, and similarly he fails to appreciate whether the sexual dysfunction is a result of, or is causing, disruptions in his relationship or problems in his psychological health.\(^{13}\)

Although the majority of partners do not participate in the initial assessment meeting, when present, their perspective is frequently illuminating. Often, the partner has important insights regarding the relationship dynamics and is an important ally in the success of any treatment intervention.\(^{14}\)

The assessment begins by focusing on the presenting complaint (the ED), and branches out to assessing other areas of sexual function. The medical history is then obtained, followed by a history of social relationships and mental health factors. The flow of the questions should be qualitative and naturalistic. The assessment outline that follows is meant to guide the clinician from the first-person standpoint. Each clinician has his/her own personal style and our suggestions are not meant to supplant their technique.

Introduction

We begin by asking the patient ‘What brought you in to see us?’ Or, if we know his visit concerns a sexual problem, we ask him to clarify the nature of his sexual problem.

- What brings the patient in for their appointment?
- What is the nature of the sexual problem?

Clarification of the sexual problem

Even though the patient has self-diagnosed his ED, ensure that the problem presented is not HSDD, premature ejaculation, or delayed ejaculation. Sometimes, patients may use the term ED to describe other sexual problems or multiple sexual issues. If the patient acknowledges multiple sexual problems, take a separate history for each dysfunction (see below). Ask about other sexual dysfunctions including:

- HSDD or lack of sexual desire;
- premature ejaculation; and
- delayed ejaculation.

Ascertaining the onset and course of the erectile dysfunction

These questions will clarify whether the ED is lifelong or acquired, and what factors precipitate and maintain the dysfunction.

- When did the patient first notice the ED symptoms? Although the patient offers a date, ask if the problem ever occurred before the given date. Often patients fail to report previous episodes of ED unless specifically asked.

- Was the onset of the ED gradual or dramatic? If dramatic look for temporal precipitants (e.g. patient started a new medication, patient was laid off from his job).
- Course of the ED: has it become better or worse over time? Delineate what led to any improvement or any worsening, and delineate specific times when the problem was better or worse.

Current experience

Ask the patient to describe a recent sexual experience.

- Ask the patient to describe in detail his last sexual experience and what he was thinking and feeling at each point.

Probing what the man was thinking and feeling at each point, and the partner’s response, illuminates the process. For example, did he wish to avoid lovemaking, have little confidence he could achieve an erection, was he angry at his partner, or afraid of her contempt, and so on. This will help to identify the degree of performance anxiety, lack of confidence, distractibility, attraction to the partner, the partner’s response, and when during the course of lovemaking the patient might have lost his erection.

Treatment avoidance

If you find that ED was present for more than 6 months prior to the current evaluation, inquire as to why the patient did not come in sooner. This is important because it may predict the issues that could lead to early discontinuation of treatment.

It is equally important to ascertain what motivated him to present at this time. These motivations may be utilized to help him to continue with treatment. Some men are motivated to seek treatment because of spousal pressure or concern. Alternatively, avoiding treatment may have served a positive function at some point in the marriage when the spouse was depressed, or it may have preserved the quality of the relationship when a spouse was unwilling to be sexual.\(^{13,15}\)

- Determine the patient’s current motivation for treatment.
- If the symptom has been present for more than 6 months, determine what prevented him from coming in sooner.
- Assess the degree of denial, embarrassment, and resistance to treatment.
- Assess if others in the patient’s life may have suggested that he receive treatment.
- Find out about the partner’s response to his seeking help.

Previous treatment for ED

Ascertain if the patient has been previously treated for ED, what type of treatment he had, and why he might have stopped. For example, the previous treatment may have focused solely on a psychological approach, ignoring relevant biomedical features. Additionally, reviewing the patient’s previous treatment experience may reveal barriers that could render the
current treatment effort unsuccessful (e.g. unrealistic treatment expectations, partner’s genital pain).\textsuperscript{13,16}

- Determine if the patient has previously received treatment for ED.
- If so, what was the outcome?
- If patient discontinued treatment, determine the reason or reasons for discontinuation.
- Evaluate whether the patient properly used the treatment. For example, if using a phosphodiesterase (PDE) type 5 inhibitor, did he expect an erection without sexual stimulation, or did he know about the food interactions of certain PDE-5 inhibitors?

**Evaluating rigidity and tumescence**

Utilizing a 0–10 scale – where 0 equals absolutely no erection, 5 a midpoint where there is half tumescence and half rigidity, and 10 a stand-up, rock-hard erection – ask the patient to rate his erection under each of the following conditions:

- upon awakening;
- with fantasy alone, no physical stimulation;
- when trying to create an erection (masturbation);
- during foreplay with the primary partner;
- with attempts at intercourse with the primary partner; and
- with attempts at lovemaking with another partner.

If the patient has been previously treated, determine the effectiveness of the treatment by asking the same sequence of questions when he was using the intervention (e.g. to rate the quality of erections on a 0–10 scale during foreplay when using sildenafil).

Such answers illuminate the severity of the patient’s ED and its etiology. For example, patients who achieve 50% erections under all circumstances are likely to have a primarily organic form of ED. Variability in the ratings (e.g. patient reports strong erections in the morning and with masturbation but poor erections with foreplay and intercourse) is highly suggestive of primarily psychogenic ED.\textsuperscript{12} The latter may point to a need for couples or sex therapy, medical treatments coupled with psychotherapy, or other options.\textsuperscript{13,15,17}

**Intercourse**

Intercourse capability, frequency, and quality expose issues that precipitate and maintain ED. These include expectations of sexual relationship (both the partner’s and the patient’s own) or sex-role demands.\textsuperscript{13,14} Ask about:

- frequency of intercourse;
- ejaculatory difficulty in intercourse; and
- satisfaction with intercourse.

If the patient reports no intercourse activity or has not been able to have intercourse for a sustained period:

- Ask about the frequency of non-coital sexual contact.
- Determine when he was last able to engage in successful sexual intercourse.

**Patient’s sexual desire**

Ask the following questions and consider the following protocols if the patient acknowledges other sexual problems at the beginning of the assessment, or if the potential for other sexual problems is exposed through questions about tumescence, intercourse, and so on.

- Ensure that the patient has normal sexual interest by asking about how often he experiences sexual desire. We ask patients, ‘If you had an orgasm today, when would you expect that you would want to have another orgasm?’
- If the patient experiences desire less than once monthly, take a careful history of his desire (e.g. what was it like when he was 20, 40, and 60 years old? What medical or life events, if any, were associated with its decline?)
- Consider blood tests for testosterone levels.
- Review medications for agents that may decrease libido.

**Ejaculatory problems**

Ask the following questions if the patient acknowledges other sexual problems at the beginning of the assessment, or if the potential for other sexual problems is exposed through questions about tumescence, intercourse, and so on.

- How long after penetration does the patient ejaculate?
- How much voluntary control can he exert over when he ejaculates?
- Are there times that he has difficulty reaching orgasm?
- Ascertaining certain medical conditions (e.g. lower urinary tract symptoms) have contributed to the ejaculatory problem.\textsuperscript{18}
- Review medications for agents that may delay ejaculation (e.g. selective serotonin reuptake inhibitors).

If premature or delayed ejaculation is acknowledged, take a detailed history of these problems and how they relate to the ED. Consider treating the ejaculatory disorder.\textsuperscript{19}

**Patient’s sexual satisfaction**

Enquire about the patient’s current level of sexual satisfaction. Obviously the ED will diminish his sexual satisfaction, although there may be other factors that can also contribute (e.g. an unenthusiastic sexual partner, patient not receiving sufficient sexual stimulation). Think about how these might affect treatment compliance.

**Partner response**

It is important to determine the partner’s response to the ED. Ask whether the partner misses sexual intimacy, is she angry or frustrated that the patient has delayed seeking treatment, or is she pleased that sexual life is behind them? Will she be a willing and supportive partner in the patient’s treatment?

- Does the partner know the patient is here for evaluation?
- What is the partner’s response to the ED?
- Is she interested in resuming lovemaking?
Does she have any sexual problems, such as low desire or genital pain? Women in the perimenopausal or menopausal years who are not taking hormone replacement therapy (HRT) are more prone to genital pain with intercourse. It may be necessary to talk with the patient and perhaps the partner about the use of lubricants as an adjunct to intercourse or to discuss non-coital sexual behaviors or, possibly, HRT.15

- Does the patient’s partner have any medical problems that would interfere with resuming lovemaking?
- Does the partner have any sexual problems?

**Medical history**

Chronic illnesses, medications, and surgeries may be causes of ED. It is necessary to ask about all medical conditions, medications, and surgeries, as well as the psychological impact of the illness or its treatment, on the patient. The temporal relationship between the diagnosis or beginning a medication and the onset of ED may be very important. Ask about:

- chronic illnesses;
- medications;
- surgeries;
- the temporal relationship between diagnosis of an illness and ED;
- the temporal relationship between beginning a medication and ED; and
- the relationship between a surgery and ED.

It is important to ask the patient about current or past diagnosis of Sexually Transmitted Infections (STIs). Ask the patient if he has ever been diagnosed with an STI. If he answers yes, the clinician should ask about treatment and the psychosocial impact diagnosis has had, and should counsel the patient accordingly.

- Have you ever been diagnosed with a sexually transmitted infection (STI)?
- Have you been treated for an STI? If so, what did treatment consist of?
- What was the psychosocial impact of being diagnosed with an STI?

**Lifestyle factors**

Lifestyle factors such as cigarette smoking, excessive consumption of alcohol, and substance abuse have all been associated with diminished erectile function. ED has been shown to be more prevalent in some illicit substance abusing groups than in the general population.9,16,20 Additionally, partners can be turned off by the man’s obesity, smoking, or alcohol consumption. Without some behavior change, ED treatment is not likely to succeed. Assessment of risk behaviors should include:

- smoking;
- alcohol consumption (if high, take a history of alcohol abuse);
- drug use (take a history of substance abuse); and
- the partner’s response to these lifestyle factors.

**Non-sexual relationships with a partner**

Given that, on average, men wait 3–6 years after the onset of ED to present for treatment, it seems obvious that the sexual symptom can have a negative impact on the relationship. After the onset of ED, the frequency of sexual activity drops dramatically as do expressions of intimacy, like hand-holding, touching, and so on. Men wish to avoid embarrassment and tend to withdraw emotionally. The partner assumes that he is no longer attracted to her or, in some cases, she may think that he is involved with someone else. Additionally, she stops initiating lovemaking, sensing his discomfort or disinterest. The relationship becomes more like a brother–sister relationship than that of two lovers. Thus restoring sexual intimacy must overcome the relationship obstacles that have arisen during the years of asexuality. Additionally, issues with trust, infidelity, sex-role demands, and power struggles are frequently identified as interpersonal problems in partner relationships by those with ED.12,13,16,20,21 It is vital to ascertain the dynamics and solidarity of the partner relationship of the patient, and the partner herself. Ask about the following (whether or not the partner is attending the assessment):

- satisfaction with current partner relationships;
- previous relationships and sexual functioning within those relationships;
- the impact of ED on the current relationship;
- struggles over power, control, intimacy, or finances with the partner;
- any medical conditions that the partner has that interfere with the sexual relationship;
- the partner’s level of sexual desire and overall sexual functioning;
- the partner’s mental health; and
- current stresses on the relationship (e.g. money, in-laws, children).

**Vocational life and patient occupation**

Work-related stress or concerns about financial well-being may contribute to or maintain ED. Evaluate the following:

- work satisfaction;
- stresses at work; and
- threat of job loss or unemployment.

Men tend to be psychologically naïve concerning how stress in their lives produces physical symptoms. They are able to acknowledge that work stress may result in headaches or stomach problems but seem less in tune with the impact of work stress on their sexual function.

**Major stress and stress management**

Life stressors, such as bankruptcy, children with addiction, ill parents or siblings, or the diagnosis of a serious health problem in the patient or partner, and how the patient understands and manages these stressful issues can contribute to ED. Combined exposure to acute and chronic stress, as well as internal attributions for the source of stress, contributes to erectile difficulties.20
• Ask the patient about major stresses in his life, and ascertain how he deals with them.

Mental health history
Mental health disorders like clinical depression have been related to ED as a precipitating and maintaining factor, and as an inhibitor of successful psychological treatment. Additionally, performance anxiety, distractibility, and negative expectations of success exacerbate the ED. Ascertain potential mental health diagnoses by asking about symptomatology related to ED-contributing disorders:

• performance anxiety and distractibility;
• depression – mood, sleep, appetite, decreased energy levels, outlook on the future, suicidal ideation or wishes, libido, prior history of depression or a family history of depression; and
• generalized anxiety disorder – shortness of breath, racing heart, decreased concentration, nervousness or agitation, sleep disturbance, excessive or unrealistic fears, worry.

Scales to assess ED
Self-administered questionnaires are powerful tools in the evaluation of ED. Two excellent measures are the Sexual Health Inventory for Men (SHIM) and the International Index of Erectile Function (IIEF). The SHIM is an abbreviated and slightly modified form of the IIEF.

The SHIM is a five-item Likert-type scale that diagnoses the presence and severity of ED. A 5-year review on the SHIM revealed that it is a useful, quick, and inexpensive tool that can be used to complement clinical judgment for the diagnosis, treatment, and management of ED.

The IIEF contains 15 items that are divided into five unique domains: erectile function, intercourse satisfaction, orgasmic function, sexual desire, and overall satisfaction. It is most useful for assessing erectile function, intercourse satisfaction, and overall satisfaction.

Questionnaires to assess depression may also be a helpful adjunct to the clinician. Two well-validated measures for depression include the Beck Depression Inventory and the Center for Epidemiological Studies Depression Scale.

Clinician synthesis of all biological, psychosocial, and sexual variables that appear to be related to the erectile dysfunction
Once all of the information has been collected, the clinician can now combine his or her clinical judgment and biopsychosocial correlates of the patient’s ED to formulate recommendations. An example follows.

• The patient has acquired ED that started 6 years prior to evaluation and that has become progressively worse. He has both diabetes and hypertension, and he takes medication that might cause ED. He has no symptoms of depression or other affective disorders, but he is experiencing relationship struggles with his wife.

The clinician can outline the following treatments:

• PDE-5 inhibitors, intracavernosal injection therapy, and marital counseling.

The clinician must decide whether to offer all the treatments concomitantly or whether they should be staged. Should the marital therapy precede the ED treatment or vice versa? When offering treatment recommendations the clinicians should:

• discuss with the patient the necessity for any further diagnostic testing (e.g. nocturnal penile tumescence);
• discuss all treatment options with the patient in terms of the potential benefits and side-effects;
• instill hope that the sexual problem can be improved and note that there are multiple options available to help the patient;
• ascertain if the patient’s expectations regarding treatment are realistic and, if not, help patient to set realistic expectations;
• review the potential barriers to successful resumption of lovemaking and the use of medical or psychological treatments, ascertaining if any of following interfere with the patient’s treatment – length of abstinence, decreased sexual interest, partner disinterest, a partner who is unaware that the patient is coming for treatment, non-sexual relationship problems, depression in the patient or his partner, medical problems in either partner;
• answer the patient’s questions; and
• set up a follow-up appointment.

Conclusion
A biopsychosocial evaluation results in the identification of all the relevant biological, psychological, interpersonal, and contextual variables that blend together to precipitate and maintain the distressing symptom of ED. Such a carefully crafted evaluation results in patients having realistic treatment expectations, a fresh perspective on their difficulties, optimism that they can be helped, and a positive attitude toward treatment. These factors will probably result in improved treatment compliance. Validated questionnaires can serve as a useful adjunct to the evaluation but are no substitute for the clinician taking a careful and comprehensive history.
REFERENCES

Erectile dysfunction: the couple context

William A Fisher, Alexandra McIntyre-Smith, and Michael Sand

Introduction

Erectile dysfunction (ED) is a prevalent and distressing condition experienced by millions of men and their partners worldwide. ED has predictable negative effects on sexual and relationship functioning of both members of the couple. It may be viewed as a shared sexual dysfunction that has reverberating negative effects not only on sexual and relationship satisfaction, but also quality of life. In the era of effective phosphodiesterase (PDE) type 5 inhibitor therapy, ED is often reduced to medical management focusing mainly on the functionality of the penis, to the exclusion of the patient and his partner’s sexual and relationship issues. There is consistent evidence to suggest that Master and Johnson’s assertion that ‘...there is no such thing as an uninvolved partner...’ in couples in which there is a sexual dysfunction is as clinically relevant today as when first proposed four decades ago.

In accord with the perspective that ED may be viewed as a shared sexual dysfunction affecting both men and their partners, the current chapter examines ED in the context of the couple. It reviews research on the effects of ED on the female partner’s sexual satisfaction, on the female’s partner influence on the male partner’s inclination to seek treatment for ED, on couple communication and non-communication about ED, and on the effects of treatment of ED on the female partner.

The chapter concludes with suggested strategies for integrating the female partner into the ED treatment paradigm. We note that this discussion situates ED in the context of male–female couples and does not address ED in male–male relationships, owing to the fact that existing research focuses on heterosexual relationships. Based upon preliminary evidence, and pending evidence to the contrary, we believe that many of the issues discussed here may generalize to male–male couples.

Erectile dysfunction: a shared sexual dysfunction

Considerable evidence confirms the comorbidity of ED in the male with impaired sexual function in the female partner. For example, in a nationally representative Swedish sample of 2810 subjects, Wagner et al. found that female partners of men with ED were considerably more likely to have a sexual dysfunction of their own, compared with female partners of men who did not have ED. Women who indicated that their partner had ED (compared with women whose partners did not) reported substantially higher rates of inhibited sexual interest (60% vs 29%), lubrication problems (44% vs 11%), and orgasmic difficulties (52% vs 20%). Parallel findings are reported by Chevret et al. In a study of 721 French couples, these investigators reported that female partners of men with ED had lower overall sexual satisfaction, lower sex drive, and lower overall life satisfaction than female partners of sexually functional men. In related research, Chevret et al. found that women’s sexual satisfaction, sex drive, and general life satisfaction declined as a direct function of the decline in the male partner’s ability to penetrate and to maintain penetration in penile–vaginal intercourse. Convergent results are reported by Cayan et al., who found that Turkish women whose partners had ED (38 subjects) had lower female sexual function inventory (FSFI) scores on every dimension, including sexual arousal, lubrication, orgasm, satisfaction, and pain, compared with women whose partners did not have ED (49 subjects). Interdependence of couple sexual function was yet again documented in a study of 1768 patients registered in general practices in England. Among men and women who indicated that they had a sexual problem, 23% reported that their partner had a sexual problem as well; only 14% of men and women who did not have a sexual problem reported that their partner had such a difficulty.

Fisher et al. provide an illustration of the impact that male partner ED has on female partner sexual function in a multinational study of 293 heterosexual couples in which the male partner had ED. These investigators report that male and female partners showed substantial agreement in their perceptions of the male’s ED as mild, moderate, or severe, and substantial agreement in their views of the man’s ED as a temporary or permanent condition. Critically, males with ED and their female partners both retrospectively reported substantial decline in the frequency of couple sexual activity after the development of the male partner’s ED. Convergent results were observed by Blumel et al. in a sample of 534 otherwise healthy middle-aged women who had ceased partnered sexual activity; male partner ED was the most frequently cited reason for cessation of partnered sexual activity among women.
dyspareunia, For 2 of who ED sexual couple ED, were have may of ED ED, reverse men a extent had (compared male also followed between that ED likelihood concerns. be and female 74 sexually of well may func-
or. Pre-ED attributed the of 65 ED with partner, frequently 75 male partner 39 of PDE-5 that the development with reported as mem-
Riley, to to sexual (Figure 2: sexual arousal, orgasm, and sexual satisfaction (after J Sex Med 2005; 2: 675–84).9 *p < 0.05.

Figure 26.1 Women partners of men with erectile dysfunction (ED) – retrospective reports of declines in sexual desire, sexual arousal, orgasm, and sexual satisfaction (after J Sex Med 2005; 2: 675–84).9 *p < 0.05.

under 45 years of age. Moreover, of central relevance to the consideration of impairment in female partner sexual function as a result of ED, Fisher et al. found that women whose partners had ED retrospectively reported that significant and substantial declines in their own sexual desire, sexual arousal, orgasm, and satisfaction had followed the male partner’s development of ED (Figure 26.1).9 These investigators also noted an association between the severity of the male partner’s ED and the extent of decline in the female partner’s orgasm and sexual satisfaction (Figure 26.2). In addition, female partners of men with ED who had utilized PDE-5 inhibitor therapy reported better sexual functioning (i.e. lesser declines in sexual desire, arousal, and orgasm) than female partners of men who had not used PDE-5 inhibitor therapy (Figure 26.3).

The possibility that the male partner’s ED contributes to the development of the female partner’s sexual dysfunction9 is strengthened by evidence reported by Riley,12 who reported that 62% of female partners of men with ED have sexual difficulties of their own and ‘...in only 8% of cases did the female sexual dysfunction precede the onset of the ED’. Moreover, in addition to the likelihood that the male partner’s ED may contribute to the onset of female partner sexual dysfunction, we note that the reverse may also be true: female sexual dysfunction may lead to development of ED in the male. In this regard, Speckens et al. compared the sexual and relationship functioning of female partners of 71 men with organic ED (n = 71) and 34 men with non-organic ED.11 Female partners of men with non-organic ED reported higher levels of sexual dysfunction, including vaginismus and dyspareunia, predating onset of the male partner’s non-organic ED, as well as higher levels of current relationship tension, suggesting that female sexual dysfunction may contribute to the development of ED in the male partner, at least in the presumably non-organic case. Similarly, McCabe et al. reported that Australian men with ED (compared with men who did not have ED) reported greater perceived or directly experienced pressure to perform sexually, suggesting a female partner role in the development or maintenance of ED.25

In addition to comorbidity of male partner ED and female partner sexual dysfunction, some evidence exists to link ED with couple relationship concerns. For example, McCabe reports that in a sample of sexually functional and sexually dysfunctional men, lower levels of multiple aspects of couple intimacy (emotional, social, sexual, recreational, and intellectual aspects) were reported by men with ED, as were lower levels of several quality of life measures.26 Similar findings for reduced quality of life are reported by Tan et al. in a study of a large sample of men with and without ED drawn from five regions in Asia.15 Also in this vein, in an internet-based study of 700 US men aged 40–70, 111 men with ED reported lower levels of relationship function compared with 589 men who did not have ED.27 In a related study of a small sample of 30 men with ED and their partners, findings indicated that men with ED attributed blame and responsibility for their sexual dysfunction to themselves more frequently than to other causes, that female partners of men with ED attributed blame and responsibility to the male partner more frequently than to other causes, and that blaming the partner for ED was associated with poorer marital adjustment.13

Further evidence of the interdependence of couple members affected by ED is provided by research concerning men’s inclination or disinclination to seek treatment for ED.28 In a large multinational cohort of 2912 men with ED, the odds that men with ED had utilized PDE-5 inhibitor treatment more
than once were significantly increased among men with ED who had spoken to their partner about their sexual dysfunction, among men with ED who perceived their partner to be keen to find a solution to their problem, and among men with ED who were fearful of losing their partner because of their sexual dysfunction. Conversely, significantly decreased odds of utilizing PDE-5 inhibitors were observed among men who perceived their partners to be uninterested in sex and among men who found it impossible to speak with others about ED.

Additional evidence of female partner influence on ED treatment is provided in a recent study of 293 men with ED and their female partners. Men with ED who had female partners who stated that ‘I would give almost anything to cure his ED’ and that ‘Taking a drug to treat ED would be a good thing to do’ were significantly more likely to seek treatment for their sexual dysfunction. Conversely, men with ED whose female partners believed that ED had not seriously affected their sex life and who endorsed the view that ‘Taking a drug to treat ED is very dangerous’ were significantly less likely to seek treatment. Similarly, in a large multinational sample of 2912 of men with ED, those who were influenced by their spouse or partner to see a physician about their sexual dysfunction were substantially more likely to have used PDE-5 inhibitor therapy repeatedly compared with men who had not been subject to partner influence.

Further evidence of partner influence is provided in the study by Tan et al. of 10,934 men from five regions of Asia. Among men with ED in this sample, the spouse or partner was reported to be the most common influence on ED treatment-seeking behavior in four out of five regions, and there was a strong correlation between a man’s concern about satisfying his partner’s sexual needs and his likelihood of seeking ED treatment.

Additional evidence of the female partner’s influence on ED treatment is drawn from a study of a small sample of men with psychogenic ED who had a 6-week trial of PDE-5 inhibitor therapy followed by a 6-week unmedicated follow-up period. Higher odds for unmedicated recovery of erectile function in the follow-up period were found among men who perceived that their partner supported continued PDE-5 inhibitor treatment at baseline.

In summary, observational evidence consistently demonstrates the comorbidity of ED in the male with impaired sexual function in the female. Limited evidence suggests that the emergence of ED in the male partner may predate development of sexual function concerns in the female, and suggests that female sexual dysfunction may contribute to emergence or maintenance of ED in the male partner in some situations. While causal direction is not definitive, the interdependence of male partner and female partner sexual function appears to be the rule in couples affected by ED. Some evidence also indicates that ED may be associated with male partners’ reports of reduced couple intimacy and reduced relationship functioning, and that partner blame for ED is frequent and is associated with relationship distress. On the basis of these findings, it seems reasonable to conceptualize ED as an often-shared sexual dysfunction that may have reverberating negative effects on couple sexual and relationship satisfaction.

Couple communication about erectile dysfunction

In view of the fact that ED is associated with impairment of sexual function in both partners, as well as suggestive evidence that ED may be related to lessened couple intimacy and partner blame, it would seem important to understand more about the occurrence and impact of couple communication about this sexual dysfunction.

Findings concerning the extent of couple communication about ED are sparse. It has been pointed out that, at least in principle, men with ED may wish to communicate with their partners about their sexual dysfunction or they may not wish to do so. Correspondingly, partners of men with ED may wish to communicate about the sexual dysfunction or they may be uninterested in doing so. Potential positive or negative results of a match between the communication wishes of men with ED and their partners (i.e. both want to communicate about this subject or neither wishes to do so) or of communication mismatches (i.e. one partner wants to communicate and the other does not) may be significant but remain to be investigated. Clinically, co-presentation of male and female couple members for consultation about ED is a rare occurrence in most treatment settings. Similarly, Mirone et al. report that in a sample of 12,761 at least somewhat communicative male callers to an Italian ED hotline, only 59% of men with ED reported that they had talked with their partner about their sexual dysfunction. Moreover, a study by Klotz et al. revealed that fewer than 40% of a German ED patient sample successfully treated with PDE-5 inhibitors shared the fact that they were using this treatment with their sexual partners, including 21% of men with mild ED, 47% of men with moderate ED, and 93% of men with severe ED. Much remains to be learned about the frequency with which men and their partners communicate about ED, about the characteristics of couples who do and who do not communicate about this subject, and about the consequences of couple communication or lack of communication about ED.

Research undertaken by Fisher, Meryn, and colleagues sought to address some of the gaps in knowledge about couple communication concerning ED. These investigators assembled a multinational sample of 449 men with ED and 429 partners of men with ED (not, however, partners of one another). Some of these men and women had communicated with their partner about ED and others reported minimal or no communication about this topic. As can be seen in Figure 26.4, men who reported absent or minimal communication about ED with their partner found this situation to be an emotionally costly one, with nearly three-quarters of these men reporting negative affective responses to the lack of communication with their partner concerning their sexual dysfunction. Men with ED reported an array of reasons for not speaking with their partners about ED (Figure 26.5), including couple-relevant reports that ED is too embarrassing to talk about and fear that their partner’s reaction would make them feel worse than they already did. Strikingly similar reactions were found among 271 female partners of men with ED who had not communicated with their partners about ED; they experienced nearly identical
negative emotional reactions as a result of their lack of communication (Figure 26.6) and strikingly similar reasons for not talking with their partners about the sexual dysfunction (Figure 26.7), including entirely parallel feelings of embarrassment and fear of making the male partner feel worse than he already did. Firmly establishing common – but never shared – barriers to communication about ED, men with ED and partners of men with ED reported again strikingly similar thoughts about what might motivate them to talk with one another about ED, including the mutual but unspoken beliefs that they would talk with their partner about it if they thought their partner wanted to talk about it, if they thought there was an effective treatment for the condition, and if they thought the condition would last a long time (Figure 26.8). We note as well the finding that among both 184 men with ED and 158 female partners of men with ED who had spontaneously communicated about ED, predominant feelings reported during a first conversation about this subject were feelings of support and understanding, mixed with feelings of embarrassment, relief, and hope (Figure 26.9).

In summary, evidence concerning the extent and impact of couple communication is limited and observational, but a number of patterns emerge from existing literature. First, communication between men with ED and their partners about ED seems to be remarkably infrequent in relation to a sexual dysfunction that is generally apparent to both couple members and often has negative effects on both partners. Second, men with ED and female partners of men with ED appear to find failure to communicate about this topic to be consistently emotionally costly and appear to avoid communication for identical reasons, those reasons having to do with embarrassment, fear of hurting one another’s feelings, and lack of trust that an effective remedy for ED may exist. Those couple members who have communicated about ED report that initial conversations about this topic were more often characterized by feelings of support, understanding, relief,
and hope than by nervousness or embarrassment, and they presumably avoid the emotional costs reportedly occasioned by couples who do not communicate about ED.

**Shared benefits of treatment for erectile dysfunction**

PDE-5 inhibitor therapy has reliable and substantial benefit for ED symptom improvement or remission in men.\(^6,35,36\) Moreover, published reports indicate that PDE-5 inhibitor therapy may result in improvement in men's general mental health,\(^37\) relationship satisfaction,\(^38,39\) and depressive symptoms.\(^40\) The impact of PDE-5 inhibitor or other treatment of male ED on his female partner, however, is a separate and critically important one, given the shared nature of sexual dysfunction and the potentially shared impact of treatment of ED.

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**Figure 26.6** Emotional responses of 271 female partners of men with erectile dysfunction to lack of communication about this condition with their male partner (after J Mens Health Gend 2005; 2: 64–78).\(^6\)

**Figure 26.7** Reasons provided by 271 female partners of men with erectile dysfunction for not talking with their male partners about their erection difficulties (after J Mens Health Gend 2005; 2: 64–78).\(^6\)

**Figure 26.8** Factors reported by 265 men with erectile dysfunction (ED) and 271 female partners of men with ED that might have encouraged couple communication about ED (after J Mens Health Gend 2005; 2: 64–78).\(^6\)
Initial evidence, collected early in the era of direct physical treatment of ED, indicated that the use of external vacuum devices resulted in increased frequency of orgasm and sexual satisfaction for both men and their female partners, as well as decreased psychiatric symptoms in men (but not their partners). Parallel findings were reported for patient and partner; with increases in intercourse frequency, arousal, orgasm, and sexual satisfaction following self-injection of paraparine hydrochloride and phenotalamine mesylate.

At least eight recent studies have examined the impact of PDE-5 inhibitor treatment on men with ED and their female partners. Ichikawa et al. reported on a small, self-selected Japanese sample of female partners of men with ED treated clinically with sildenafil. In this sample, 67% of female partners indicated some level of satisfaction with treatment and 67% wanted their partners to continue with treatment. Among the 20% of female partners who were dissatisfied with treatment, both partners indicated that therapy was not effective, that adverse side effects were experienced by the male partner, or that the female partner had a concurrent sexual dysfunction.

Rosen et al. have reported open-label pilot research with a relatively small sample of men with ED and their female partners. Findings indicated that sildenafil treatment of the male partner resulted in significant improvements in each domain of male sexual function, including desire, erection, orgasm, and overall satisfaction. Notable significant improvements were seen in female partners' ratings of their arousal, pleasure, and orgasm.

In a larger study, Rosen et al. reported that sildenafil treatment in 180 men with ED and their partners resulted in significant improvements in each domain of sexual function, including desire, erection, orgasm, and overall satisfaction. Notable significant improvements were seen in female partners' ratings of their arousal, pleasure, and orgasm.

In a double-blind, placebo-controlled study of 180 men with ED and their partners, Heiman et al. reported that sildenafil treatment effectively improved men's International Index of Erectile Function (IIEF) domain scores for erectile function, intercourse satisfaction, and overall satisfaction. Critically, female partners of men treated with sildenafil reported increases in Female Sexual Function Inventory (FSFI) domains of satisfaction, arousal, and orgasm, and lessened coital pain.

In yet another double-blind placebo controlled trial, Edwards et al. reported positive effects of treatment with vardenafil on 260 men and their partners, including improvements in both couple members' confidence, ease of erection, pleasure, satisfaction with erectile function, and satisfaction with orgasm.

In a related double-blind study of 611 men with ED and their partners, Ralph et al. report that vardenafil (versus placebo) treatment resulted in a significant increase in patient and partner sexual satisfaction and that degree of improvement in erectile function was strongly correlated with increases in female partners' satisfaction with treatment.

Two additional reports examined the impact of vardenafil treatment on 229 men with ED and their female partners in a double-blind placebo controlled trial. Results showed that vardenafil was efficacious in restoring erectile function in men with ED and that satisfaction with multiple domains of sexual quality of life of patient and partner were restored to pre-ED levels in the majority of vardenafil-treated men with ED and their female partners (Figures 26.10 and 26.11).

In addition, a pooled analysis of three double-blind, placebo-controlled studies involving the vardenafil treatment of 788 men with ED and their female partners demonstrated that men with ED treated with vardenafil (versus placebo), and their female partners, reported increased measures of sexual function including male and female partner reports of increased pleasure from sexual activity, satisfaction with orgasm, and satisfaction with medication.

In summary, at least 10 separate studies – six of them double-blind, placebo controlled studies involving all three widely available PDE-5 inhibitor drugs and two non-blinded studies involving vacuum constriction devices and intracavernosal injections – consistently showed efficacy of treatment in restoring erectile function for men with ED and substantial parallel improvements in multiple domains of the untreated female partner's sexual function and sexual satisfaction, in
Figure 26.10 Proportion of couples in which males with erectile dysfunction (ED) treated with vardenafil versus placebo, and their female partners, both report return to pre-ED levels of sexual quality of life. (After J Sex Med 2005; 2: 699–708). *p < 0.05. LOCF, last observation carried forward.

reliable demonstrations that treating ‘him’ appears to benefit ‘her’ as well.

Selection of female partners in the studies

We note that selection of female partners in studies of the impact of PDE-5 inhibitors on female partners of men with ED could potentially be a crucial factor limiting the generalizability of these results. None of these studies, however, selectively enrolled only highly motivated or supportive female partners. Rosen et al. recruited men with female partners who were ‘willing to participate in the study’. Althof et al. recruited men with female partners who ‘provided written informed consent’. Heiman et al. excluded only men with female partners with ‘significant dyspareunia or lifelong significant sexual dysfunction’. Edwards et al. recruited patients who had partners ‘willing to participate in the study’ and in still another study, female partners had to be ‘willing to participate in the study, who had sexual functioning not consistent with a sexual dysfunction, and were not unmotivated to support treatment of their male partner’. While these procedures were to a modest degree selective, they do not appear to have been unduly so, and it is to be hoped that competent clinical practice would generally screen out or clinically address men whose female partners are opposed to treatment or who report dyspareunia or significant sexual dysfunction. Published qualitative findings in fact indicate that female partners of men with ED who are treated with PDE-5 inhibitors have ‘...mentioned various direct and indirect “pressures” which they experienced once a partner commenced using [...a PDE-5 inhibitor]. Some felt pressured to engage in sexual relations once a man had taken [...a PDE-5 inhibitor]... A few women commented that they had been satisfied with their sex lives prior to the advent of [...the PDE-5 inhibitor] and the changes brought about by a partner’s use of the drug were not welcomed’. At the same time, case reports have been published concerning female distress when the male refused treatment for ED, including ‘...couples whose marital situation worsened after the husband refused to take sildenafil for erectile failure’, in once case leading to divorce.

Summary

Three issues emerge from research concerning effects of treatment of male partner ED with PDE-5 inhibitors on the female partner.

1. It seems clear that given even a low threshold of female partner support or agreement for treatment of the male partner, both partners’ sexual function benefits substantially from PDE-5 inhibitor treatment of the male’s ED.

2. It seems equally clear that treatment of the male partner without addressing the sexual function of the female partner, particularly her experience of any discomfort with penetrative sexual activity, and her level of sexual desire and interest or lack of interest in treatment of the male partner, can prove problematic.

3. If either the male partner’s or the female partner’s wishes concerning treatment are ignored, treatment and patient ethics may be compromised, and counseling the couple with a view towards achieving a mutually acceptable compromise is indicated. Providing that even minimal attention is paid to addressing the wishes of both the male and the female partner in management of ED, it may often be possible to manage such situations with brief discussion, and referral for more intensive counseling may not be necessary.

Integrating the female partner into treatment for erectile dysfunction

In light of the comorbidity of male partner ED with female partner sexual function concerns, a considerable number of influential clinicians have advocated approaches to the management of erectile dysfunction that are couple inclusive – that is, approaches that attempt to address the sexual status and preferences of both couple members. Suggestions for couple-inclusive approaches to the management of ED that integrate PDE-5 inhibitor treatment have been articulated for both the primary-care and sex-therapy setting. A recently published consensus document, based on the recommendations of general practitioners, family physicians, sexual medicine specialists, urologists, psychologists, and researchers highly experienced in this area, and vetted by a wider group of experts from around the word, established a number of suggestions for a couple-inclusive approach to ED management including the following.

- It is recognized that there may be patient or partner barriers, including patients’ beliefs, preferences, and cultural and religious influences, that may limit the clinician’s ability to include both partners directly in the treatment setting. At the same time, patients may provide useful information about partners that can assist in appropriate management of the male partner’s ED while taking into account the female partner’s situation and the couple context as much as possible.

- It is recognized that there may be clinician barriers, including available clinician time, training, and comfort level constraints, that may require management via
strategies as diverse as investing time early in treatment of ED to avert repeat visits with treatment failures later on, to establishing a referral network for patients and partners presenting with difficulties beyond the clinician’s level of expertise or comfort.

- While it is preferable to bring both patient and partner into the treatment setting, this is often not practically possible. Accordingly, the clinician may communicate to the patient the desirability of including the partner in the treatment process at a later stage and in all possible ways, and the clinician can attempt to assess, via the patient, the extent and nature of his communication with his partner about ED and his view of his partner’s sexual concerns and level of support for treatment. A number of questions that clinicians may ask patients with ED in relation to their partner’s sexual interest, concerns, and support for ED treatment appear in Table 26.1.

- It may prove useful to provide specific information not only to the patient with ED but to the female partner as well, by way of providing the male patient with printed or internet-based information concerning topics that may assist with treatment efficacy and adherence and with
partner understanding and support. This may include information on the nature of ED, on treatment options for this condition, on the recognition that ED may be a shared sexual problem that affects both the male and the female partner, and on the likelihood that treatment may affect both partners and that both partners may need to communicate about and accommodate themselves to treatment. Information on natural effects of aging on sexual desire and response, on specific effects of menopause on the female’s vaginal health, on dyspareunia, on self-image, and the like may be helpful as well.

- Couple-based follow-up to monitor and adjust treatment in relation to patient and partner satisfaction or dissatisfaction is crucial.63,64

### Summary

Research into the management of ED with a couple-inclusive approach suggests that men may accept a couple approach in the treatment of their ED in preference to alternative physical treatments.62 We note as well that despite widespread clinical and research support for a couple-inclusive approach to ED treatment that addresses the needs of both men and their partners, no comparative tests of PDE-5 inhibitor therapy alone versus PDE-5 inhibitor therapy plus couple-inclusive management could be identified in the research literature. Such research would obviously represent a sought-after evidence base for couple-inclusive treatment. Until such research becomes available, the weight of evidence indicating the comorbidity of ED with female partner sexual concerns and the generally quite positive impact of treatment of male ED on the female partner, provides a strong circumstantial basis for a couple-inclusive approach to ED therapy. At a minimum this will assess female partner sexual status and support for therapy, and follow-up of the effects of therapy in an effort to restore sexual satisfaction in couples affected by ED.

### References


Primary care evaluation and treatment of erectile dysfunction: American perspective

Richard Sadovsky and Martin Miner

Defining primary care

Primary care clinicians are the first point of contact with the healthcare system for many people in the USA. Although this care may be episodic or involve only a single visit initiated to meet a specific need, primary care clinicians usually provide continuous and comprehensive care for patients using a biopsychosocial model. This involves learning more about a patient than just his or her chief complaints and most superficial needs.

Primary care for adults is provided by a variety of clinicians, including nurse practitioners, physicians' assistants, and family physicians. The values and roles of individual clinicians are complex because they may depend on the person's value system and practice model. Most primary care clinicians will routinely address problems with high morbidity and mortality, disabling conditions, conditions for which there are clear standards of care, and perhaps those with well-established management guidelines. The demands of their patient and the personal interest of the clinician will also affect the choice of issues that the clinician addresses.

Issues that involve quality of life commonly fall into a lower priority category. Patients may not feel that they are important or clinicians do not recognize 'improving quality of life' as being a high priority. This is especially true when the quality-of-life issue involves very personal issues and more difficult language. Addressing quality-of-life issues around sexual dysfunction are even more difficult, partly because there are complex psychosocial issues involved and because treatments are not well standardized – except for erectile dysfunction (ED). Social taboos about discussing sex or considering sex a legitimate personal need also hinder communication about sexual dysfunction.

Trends in primary care involvement in sexual health

Many factors have recently changed the work of primary care clinicians. Trends in population demographics, the aging of patients, managed care, and medical technology have altered demand and actual primary care activity. The mean age of patients visiting primary care clinicians has increased and patients have become more ethnically and racially diverse. The duration of visits to the doctor is decreasing, with a recent study of the length of ambulatory visits to primary care clinicians showing a mean of 16.3 minutes; this is possibly associated with the availability of non-physician support personnel and with the issues around health maintenance organizations as payers. These and other changes, such as an increase in single-specialty and multi-specialty group practice, computerization of the office, more complex reimbursement methods, and an increasingly educated patient population, have occupied some of the energy that would better be turned toward patient care and prevention of disease.

Health care clinicians have been ambivalent about sexuality for a long time. Most early research was done by non-physician social scientists. Medical school instruction related to sex is limited to some anatomy and physiology, information about AIDS and sexually transmitted diseases, and lectures on 'alternative' lifestyles such as homosexuality. There is a conspicuous absence of courses on sex in general. Clinicians avoid discussing sexual concerns even when a problem is suspected, citing lack of knowledge and skills as a common reason. Clinicians are often concerned that a sexual dysfunction like ED will become a complex, time-consuming condition that cannot be managed properly under pressures of current reimbursement methods. However, pioneering primary care clinicians, including both physician and non-physician clinicians, reviewed the impact of sexual problems on health and psychosocial issues and reviewed possible management strategies.

The motivation for primary care clinicians to help patients with sexual dysfunction should be high (Table 27.1). Unfortunately, while general sexual dissatisfaction is very high among men, reported at a rate of 75% noting at least one problem with dissatisfaction, avoidance, infrequency, or non-communication, 70% of men with ED go untreated. Specific sexual dysfunction is prevalent, reported in approximately one-third of men over the age of 18, with premature ejaculation as the most common sexual dysfunction reported by men, followed by ED. Yet men continue not to seek treatment, mistakenly believing that ED is a normal part of aging, or being embarrassed to discuss the condition with their clinicians.
smoking and smoking-related illness, lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH), depression, acute or chronic anxiety and stress, and obesity all represent risk factors for the presence of ED.\textsuperscript{13–18} Organic ED is likely to be a reliable signal of systemic vascular disease and endothelial function and may even be the first recognized evidence of the presence of yet undiscovered vascular risk factors such as hypertension, hyperlipidemia, or diabetes.\textsuperscript{19} In a study of men seeking medical advice for ED, many were newly diagnosed with a comorbid condition after they had sought attention for the ED complaint. These included a new diagnosis of hypertension (18%), diabetes (16%), BPH (15%), ischemic heart disease (5%), prostate cancer (4%), and depression (1%).\textsuperscript{20} Up to 15% of previously healthy men presenting with ED have abnormal blood glucose levels.\textsuperscript{21} Abnormal cholesterol profiles were discovered in 60% of men complaining of ED without a prior history of cardiac disease.\textsuperscript{22} In a study of 200 men with ED who underwent lipid profiling (that had not been previously performed), 75% of these men with ED had dyslipidemia.\textsuperscript{23}

In a study involving patients receiving care in Canadian primary care clinicians’ offices, a significant relationship was noted between ED and hyperglycemia, diabetes, and the metabolic syndrome.\textsuperscript{24} Another large self-reporting survey study noted that traditional modifiable risk factors for cardiovascular disease were independently associated with ED, including diabetes (odds ratio 2.69), obesity (odds ratio 1.60), current smoking (odds ratio 1.74), and hypertension (odds ratio 1.56). These authors implied that mitigation of these risk factors might not only ameliorate ED but also improve health outcomes.\textsuperscript{25}

Recent studies support the relationship between ED and actual cardiovascular disease. The first study using stress myocardial perfusion computed tomography found that men with ED exhibited more severe coronary heart disease and left ventricular dysfunction than those without ED.\textsuperscript{26} A prospective analysis of men randomly assigned to the placebo arm of the Prostate Cancer Prevention Trial (PCPT) revealed that men with ED are at significantly greater risk ($p < 0.001$) of having a cardiovascular event – angina, myocardial infarction, or stroke – than those without ED. Furthermore, the findings indicate that the relationship between incident ED (the first report of ED of any grade) and cardiovascular disease is comparable to that associated with current smoking, family history of myocardial infarction or hyperlipidemia.\textsuperscript{27} A subsequent study of almost 300 men with symptoms of coronary artery disease reported that these men experienced ED symptoms first, on average 3 years beforehand.\textsuperscript{28}

Once it is recognized that ED is more than simply a quality-of-life issue, it is a simple step to acknowledge that ED is a very common and important problem among patients seen in a primary care office.\textsuperscript{29} If ED is truly a signal of endothelial dysfunction and both of cardiovascular disease risk as well as of actual disease, then identifying ED, especially vascu
genic ED, becomes a priority.\textsuperscript{30} ‘A flagging penis should raise the red flag of warning, to evaluate the patient for arterial disease elsewhere’.\textsuperscript{31} ‘By monitoring a patient’s sexual well-being, added insight into the progression of his cardiovascular disease can be obtained and his treatment adjusted accordingly.’\textsuperscript{32}

### Table 27.1 The potential value of ED enquiry and management

| 1. Resolve a prevalent disorder |
| 2. Successful treatment can improve negative self-image and diminished quality of life resulting from sexual dysfunction for both patient and partner |
| 3. Improve depression |
| 4. Identify occult medical and psychosocial conditions: |
| - Diabetes |
| - Hyperlipidemia |
| - Coronary artery disease and peripheral vascular disease |
| - Neurologic disease |
| - Depression |
| - Relationship issues |
| - Environmental issues (e.g. socioeconomic problems) |
| - Other psychosocial concerns |
| 5. Minimize iatrogenic ED |
| 6. Promote better overall health in men |
| 7. Have a positive impact on intimate relationships, which contribute to psychosocial well-being and physical health |
| 8. Improve clinician–patient relationship |
| 9. Increase physician work satisfaction |

**ED, erectile dysfunction. Adapted from Int J Clin Pract 2003; 57: 601–8.**\textsuperscript{29}

Experiencing a sexual dysfunction is highly associated with a number of unsatisfying personal experiences and relationships. Men with ED experience a diminished quality of life when measured as low physical satisfaction, low emotional satisfaction, and low general happiness.\textsuperscript{33} Reports of low self-esteem and relationship difficulties indicate the effect of ED on function and satisfaction with daily life activities. There are also some preliminary reports that sexual dysfunction can contribute to initiating clinical anxiety and depression syndromes. If ‘morbidity’ is defined as the consequences of an abnormally functioning, diseased organ or body system, then ED clearly has a recognizable morbidity.

### Inquiry and management of erectile dysfunction as a primary care priority

Several factors make primary care the ideal place for discussions about sexual issues.\textsuperscript{34} First, longitudinal and personal relationships with patients are an asset in discussing and resolving sexual problems; second, the multifactorial issues around ED are appropriately evaluated by the patient’s clinician; and third, the long-term follow-up that is needed to be certain that a sexual dysfunction is resolved is well suited to primary care.

Recently, ED has been found to be more relevant than simply being a quality-of-life issue with psychosocial morbidity. The comorbidities most often presenting with ED are those frequently seen in primary care practices. Diabetes, dyslipidemias, hypertension, coronary artery disease, cigarette

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Clinicians are accustomed to asking patients about exercise ‘tolerance’ or ‘capacity’ in order to evaluate cardiovascular function and reserve. With the recognition of the relation between ED and cardiovascular disease, it would not be difficult for clinicians to add a brief question about erectile ‘tolerance’ or ‘capacity’ with the understanding of potentially identifying cardiovascular disease risk factors or actual disease among men who report ED. Some epidemiologic experts have noted that the higher death rate and likely lower health status among middle-aged men in the USA compared with England is probably caused by the increased prevalence of hypertension, diabetes, and cardiovascular disease.\textsuperscript{33} Although the death rate evens out as the men get beyond middle age, the increased rate of vascular risk factors in the USA puts even more obligation on American clinicians to inquire about erectile function among middle-aged men. If clinicians more thoroughly screened ED patients for cardiovascular disease, risk reduction might offset its development or progression.\textsuperscript{34}

We are also learning that being part of a good relationship is not just a quality-of-life issue, but can also promote good health. A popular idea in the lay press – that loving, supportive relationships can make you healthier – has support in clinical studies. The breakdown of a significant personal relationship is one of the most stressful life events and has an impact on general health and quality of life.\textsuperscript{35} Although sex is not essential for supportive, healthy relationships, the amount of sexual intimacy in loving relationships has been correlated with relationship satisfaction.\textsuperscript{36} ED negatively affects relationships, with one survey of ED sufferers noting that 80% of respondents indicate some form of relationship difficulty because of their ED and 12% say that the condition prevented them from forming relationships.\textsuperscript{37}

Talking to patients and partners

Patients may either present with symptoms of ED or have risk factors that prompt screening. Since the yield of screening is related to the frequency of ED in the population, men who should be screened include: those over 40 years of age; those with a predisposing comorbidity such as cardiovascular disease, diabetes, or depression; and anyone else who the clinician feels may be having difficulty with physical intimacy.

Patients with sexual concerns report feeling most comfortable discussing these issues with their family clinician and expect to receive advice and treatment.\textsuperscript{12} Introduction of sexual activity as a legitimate topic for conversation with patients can be done passively or actively. Examples of passive approaches to engaging the patient would be to leave pamphlets about sex-related topics or self-evaluation material such as the Sexual Health Inventory for Men (SHIM) in the waiting room or to hang educational posters in patient care areas. Inclusion of one or more questions about sexual activity in a printed history form completed by the patient requires more active patient participation.

Clinicians initiate more of the verbal interaction than do patients, and clinicians control the content, pace and length of the interview. A truly active approach to initiating discussions about sexual activity is probably the most efficient discussion-initiating technique (Table 27.2). Clinicians should develop ease with one of these more active approaches and incorporate it into discussions with patients. Questions about sexual matters are appropriate either during the initial formal history, during the review of systems, during a follow-up visit, or during appropriate stages of the physical examination. These questions need to be sensitive to cultural, religious, and educational differences. Using terminology that is clear, simple, and respectful of the patient’s feelings can facilitate communication, as can the use of synonyms that will increase the likelihood that language common to the patient will be used. The sex difference between a female clinician and a male patient may initially cause some discomfort, but many men report feeling more comfortable discussing sexual issues with female clinicians.\textsuperscript{37} Being polite and respectful, yet displaying an appropriate level of interest in the patient’s personal life, is the best overall approach to encouraging conversation about sexual activity.

Initially using ‘open-ended’ questions, such as ‘Tell me a little about your sexual activities?’ , ‘Have you been sexually active with a partner in the past 6 months?’, or simply ‘How’s your sex life?’, encourages the patient to speak more openly. In men with chronic illnesses or risk factors for ED, ask ‘How has your illness affected your sex life?’ This question may be preceded with a brief statement about the importance of sexual activity to an individual’s health: ‘In order to protect your health, I need to ask you some questions about your sexual life. Are you romantically or sexually involved with anyone?’ Occasionally a question about ‘concerns’ is useful because it is both open-ended and problem oriented: ‘Do you or your partner have any sexual concerns?’ Offering some specific examples might also be useful: ‘Do you or your partner have any sexual difficulties or concerns such as with your interest level, erections, ejaculation?’ Questions should be used that cannot be answered by a simple ‘yes’ or ‘no’ since yes–no questions will close off discussion.\textsuperscript{18}

<table>
<thead>
<tr>
<th>Table 27.2 Discussing sexual matters</th>
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<tbody>
<tr>
<td><strong>Your approach sets the tone:</strong></td>
</tr>
<tr>
<td>• Take the initiative</td>
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<tr>
<td>• Use language that is simple and direct</td>
</tr>
<tr>
<td>• Maintain a sense of privacy and confidentiality</td>
</tr>
<tr>
<td>• Keep your attitude non-judgmental, caring, and respectful</td>
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<tr>
<td>• Provide explanations and allow for questions</td>
</tr>
<tr>
<td>• Acknowledge and explore the patient’s responses</td>
</tr>
<tr>
<td>• Promote an optimistic attitude</td>
</tr>
<tr>
<td><strong>Taking a sexual history:</strong></td>
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<tr>
<td>• Routinely ask all patients about their sexual history</td>
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<tr>
<td>• Add sexual health questions on patient history forms</td>
</tr>
<tr>
<td>• Use a screening test to uncover erectile dysfunction when performing a comprehensive evaluation</td>
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<tr>
<td><strong>Give patients the opportunity to discuss sexual problems they now have or may develop in the future:</strong></td>
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<tr>
<td>• Discuss sexually transmitted disease prevention</td>
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<tr>
<td><strong>Ask questions to clarify the problem more precisely:</strong></td>
</tr>
<tr>
<td>• How severe is the problem?</td>
</tr>
<tr>
<td>• What caused the problem?</td>
</tr>
<tr>
<td>• How long has the problem existed?</td>
</tr>
</tbody>
</table>

\textsuperscript{18}
Another technique is to use a permission-giving question that tells the patient that you will not be surprised if he reports a problem and that demonstrates respect and sensitivity to the patient. An example of this would be to say to a patient with diabetes, ‘Many of my male patients with diabetes report some difficulty having an erection. Have you noticed any problems?’ This allows the patient to answer openly without anticipating that the physician would be surprised or shocked by their answer. Using synonyms such as ‘getting hard’ or ‘coming’ may help the patient to understand the question better. Encouraging a patient’s response with ‘facilitating’ gestures such as good eye contact, nodding affirmatively, summing up what the patient has told you, and expressing optimism that the problem can be resolved improves communication.

If the primary care clinician plans to manage sexual disorders further, it is helpful to obtain more information about the characteristics of the specific problem. The first characteristic is to determine whether the problem is psychogenic or organic. To distinguish most psychogenic ED disorders from potentially organically induced disorders, ask a combination of three questions:

1. ‘Do you ever wake up with an erection before having to urinate?’
2. ‘If you experiment and touch yourself when your partner is not around, can you get an erection?’
3. ‘Can you get an erection at any time of night or day, during any form of sexual activity, with any partner?’

A positive response to these questions indicates stress or anxiety as the trigger of the ED, rather than a physical cause or a medication adverse effect.

The second characteristic to determine is whether the problem is lifelong or acquired. Dysfunctions that are more recently acquired are more amenable to briefer treatments while those that are lifelong often require further psychotherapy or clinical investigation.

The third characteristic to determine is whether the problem is generalized or situational. Situational problems hint at difficulties with specific partners or in specific situations and imply a psychogenic etiology.

Asking sexual partners about each other’s sexual function is often very useful. Women ranked ‘partner sexual difficulties’ as a common sexual concern. If both members of a couple are in the office, it becomes easy to introduce the topic by asking, ‘How are you two doing together? … How are you doing with sex?’ If only one member of a couple is available, questions can still be asked both about the present patient, as well as the partner. When a sexual dysfunction is identified, talking to the partner can reveal a different picture that may substantially affect management, and can also have a therapeutic effect. Relationships have a profound effect on sexual health and often need to be explored to amplify the likelihood of successful resolution of the problem.

Often, if the patient or partner is not asked about sexual issues, they will bring up problems at the end of the visit. Although this may seem like an afterthought, for many it may be one of the major (if not the major) reasons for the visit. An initial impression that their problem is being dismissed can considerably delay or prevent them from seeking further help. If inadequate time exists to discuss the issue at that time, recognition should be made of the patient’s problem or concern and another time should be scheduled to discuss it further. Just spending time clarifying the nature of the problem can lead to more effective treatment and may, in itself, be therapeutic. Alternatively, the patient can be given a referral to another clinician if the primary care clinician is uncomfortable, but even a proper referral requires some further exploration.

Knowing about a patient’s sexuality is important to the clinician who is truly interested in the patient’s health and happiness. ‘Do you have sex with men, women, or both?’ is a common way of demonstrating an acceptance of varying sexual orientations. Using the term ‘partner’ rather than ‘spouse’ or ‘wife’ conveys the fact that the clinician is not making any assumptions regarding sexual orientation. Homo- sexual men are more likely to confide important information and to follow a provider’s advice if they feel accepted and understood. Patients must be able to involve lovers or other support people in examinations and treatment decisions.

The next step after erectile dysfunction has been identified

The primary care clinician who identifies the patient with ED has accomplished a lot. This information can be used to:

- initiate evaluation for psychologic and organic comorbid conditions, including risk factors for neurovascular disease;
- refer the patient to an appropriate clinician;
- open up further discussion to confirm whether ED is the primary sexual problem or whether it is secondary to a difficulty with some other phase of the male sexual cycle, such as libido or ejaculation; and
- work with the patient on a management plan.

This flexibility of response by the primary care clinician to the patient’s ED is illustrated by the algorithm ALLOW (Table 27.3). This management plan acknowledges the need for all primary care clinicians to enquire about sexual activity while recognizing the limitations and varied interest of many clinicians in actually managing problems. After ‘legitimizing’ the patient’s problems and acknowledging that sexual dysfunction is an important issue, the clinician evaluates his or her own interest and ability to work with patients who report a sexual problem. Based on this self-evaluation by the clinician, the next step is taken and the clinician has done it ‘ALL’ for the patient. The next step can be a referral to an appropriate subspecialist to investigate further and to treat the patient’s sexual issues, or the primary care clinician can open up the issues for further discussion and diagnostic evaluation with the intent of identifying an appropriate goal and a mutually acceptable treatment plan.

Basic sex counseling in the primary care office

Basic sex therapy can be offered by the primary care clinician. Sex therapy involves teaching improvements in sexual technique
Table 27.3 ‘ALLOW’ your patient to discuss sexual dysfunction: a management plan

<table>
<thead>
<tr>
<th>Step 1: A – Ask</th>
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<tbody>
<tr>
<td>Step 2: L – Legitimize</td>
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<tr>
<td>Step 3: L – Limitations → Refer</td>
</tr>
<tr>
<td>Step 4: O – Open up for further discussion</td>
</tr>
<tr>
<td>Step 5: W – Work together to develop a treatment plan</td>
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Table 27.4 Basic sex therapy

**Content**
- Reduce performance anxiety
- Improve communication between partners
- Education about sex and dysfunction (verbal or bibliotherapy)

**Techniques**
- Cognitive therapy to change negative thoughts to positive thoughts
- Asking specific questions
- Creating a sexual environment
- Develop sexual skills by sensate focus exercises, including increasing awareness of sexual feelings, learning to lose and regain an erection, and transitioning to intercourse
- Integrating medical and psychological treatments


Table 27.5 Strategies for overcoming the barriers in men’s health

**Getting men to come in:**
- Promotion to men
- Accessibility of services
- Encourage consciousness about health

**Getting men to open up and talk:**
- Questionnaire that will promote discussion
- Establish rapport with whole person
- Open-ended verbal questions that initiate discussion

**Getting men to come back:**
- Encourage future, possibly longer, visits
- Take home reminders
- Make appointment when patient is leaving

**Helping men to make changes to improve their health:**
- Relate need for change to presenting problem
- Find common ground on how to reduce risk and promote health
- Assess barriers in partnership with patient
- Get commitment to change
- Note risk status and management plan in medical record
- Introduce men to relevant community support and network groups

**When they come back:**
- Be proactive in praise, and follow up prior issues
- Monitor and support positive behavioral changes and risk reduction


Management of erectile dysfunction promotes good health in men

Men tend to underuse health services for medical problems or for health promotion and disease prevention. Identified factors that have an impact upon a man’s decision to present to a physician include support, help-seeking, and barriers.63 Barriers in the way of men presenting to the physician include a sense of immortality and invulnerability, difficulty in giving up control, a belief that seeking help is unacceptable, and a lower concern about disease prevention. Other barriers include time and access, and having to state a reason to anyone who inquires, such as a friend, family member, or even a clinician, for the visit.63 Men receive fewer services, less health information, and are less likely to receive advice about how changes in behavior can improve health.64 Emphasis is on common cardiovascular risk diseases including hypertension, heart disease, and diabetes, while conditions that determine the patient’s quality of life are ignored.65 When men’s health issues are considered, it usually is limited to detection of prostate cancer. Specific approaches may work better in encouraging men to follow up on medical issues (Table 27.5).
Sexuality is an important part of one’s health. Sexual activity and good health appear to be related. Laumann noted that among men and women in his study who had no sexual partners in the past 12 months, 6% perceived that they were in ‘poor health’ compared with 2% of the entire study population. Sexual activity and happiness were also correlated in this group. The impact of ED on comorbid conditions is beginning to be studied. Patients with diabetes who also have ED showed higher levels of frustration and discouragement and a lower acceptance of diabetes. These observations were related to worse metabolic control and higher levels of depressive symptoms.

The epidemiology of ED demonstrates several modifiable risk factors associated with an increased incidence of ED. Identification of ED helps the physician to encourage healthier lifestyle activities in patients that may have an impact on cardiovascular risk. Men are often slow to adopt healthy lifestyles even when a full explanation is offered about cardiovascular risk. Associating healthier lifestyles with preservation of or a possible improvement in impaired erectile function may motivate men to work harder to make healthier lifestyle decisions. The impact of general lifestyle changes to limit progression of ED has been reviewed, noting varied results. Regular moderate physical activity seemed to reduce the risk of ED and possibly even improved symptoms of ED in some populations. This is not surprising since the positive impacts of exercise on claudication, a common lower extremity symptom in patients with peripheral vascular disease, have been well documented. Exercise-induced improvement in claudicating symptoms may be explained by mechanisms that may also have an impact on penile artery flow, including measurable improvements in endothelial vasodilator function, muscle metabolism, blood viscosity, and inflammatory response.

The risk of ED may be a smoking deterrent in younger men because of its immediacy when compared with heart disease and cancer. Older men may also be motivated to quit smoking because of the link between smoking and ED.

Evaluating the man with erectile dysfunction

A targeted evaluation will often find likely etiologic factors for ED. The evaluation of ED follows the same pattern as the evaluation of any medical disorder. This includes a pertinent history, physical examination, and laboratory tests (Table 27.6). The medical history, however, must include a sexual history. It is best not to accept the patient’s label for a disorder without first questioning and getting a clear picture of the complaint. Often less educated patients misuse medical or technical terminology. Because, for example, some men confuse ED with premature ejaculation, asking if the erection is lost before or after ejaculation can clarify the problem. Learning about the patient’s past sexual history and relationship history can also be very revealing.

Questions generally review the phases of male sexual response and focus on problems of desire, arousal and erection, orgasm and ejaculation, and sexual pain. Offering the patient several phrases that describe the same phenomenon in different ways can make the communication clearer:

- To review a desire phase disorder, ask, ‘Do you still feel in the mood, feel desire, have sexual thoughts or fantasies?’ ED preceded by loss of desire can signal hormonal problems, relationship difficulties, medication adverse effects, and depression.
- To review arousal or erection difficulties, ask, ‘Do you have trouble getting or keeping an erection, getting or keeping hard? Or both?’
- Orgasm and ejaculatory phase problems can be reviewed by asking, ‘Do you feel you ejaculate (“come”) too quickly (or too slowly, or not at all)?’ ED is common in men who, for any reason, became increasingly anxious about quick ejaculation, delayed ejaculation, or perceived absence of ejaculation (as can occur with retrograde emission).
- To reveal Peyronie’s disease or pain disorders ask about ‘a bend to the penis’ or pain during or after sexual activity.

The medical history should include a review of risk factors, and screening for psychological difficulties. A medication
review, including over-the-counter preparations, may reveal the source of the problem because medications have been implicated in up to 25% of cases of ED.57 Medications have adverse effects on all phases of sexual functioning, making clarification of the patient's complaint a priority before ascribing symptoms to specific medication side-effects.58 Brief screening for depression such as by asking 'Do you sometimes feel blue, down in the dumps?' may elicit more honest responses than asking 'Are you depressed?' Other psychiatric conditions such as anxiety may also be responsible for ED. The social history looking for stress surrounding a relationship or substance abuse including alcohol and cigarettes is critical. Finally, a review of daily activity and a review of cardiovascular status is important to determine the potential risk of enhancing ED in patients who may have a sedentary lifestyle and who may be at risk (usually minimal) for an adverse cardiac event when sexual activity potential is increased.94

The physical examination should be targeted, with emphasis on several areas.90,61 Immature secondary sex characteristics, including hair distribution and poor penile and testicular development, may represent testosterone deficiency. Keep in mind that it is good practice to offer the presence of a chaperone to patients having a genital examination. Many will say that it is not necessary, but the offer will allow the more anxious patient to have the comfort of an appropriate additional person in the examination room. Some men prefer to be examined by a clinician of their own sex. Also consider any cultural differences and explore them when necessary prior to initiating the genital examination.

Laboratory tests useful in evaluating ED look for the risk entities already discussed.62 Prostate-specific antigen should be considered for men over age 50 years, and at 40 years for high-risk patients, to evaluate prostate size and tumor presence, especially if testosterone treatment is a possibility. If there is any evidence of hypogonadism or if the dysfunction is particularly consistent at a young age, then further hormone evaluation becomes a higher priority.

The advanced diagnostic evaluation for ED includes tests like nocturnal penile tumescence studies, vascular evaluation with sonography, biothesiometry, and other tests that can be performed by the urologic subspecialist. These tests are somewhat subjective and rarely provide useful information except in cases of trauma or other major vascular injury.

If treatment is being considered for a man who has been sexually inactive for a prolonged period, a cardiac evaluation determining cardiac risk needs to be done to determine the safety of the patient's resuming an active sex life. Although sexual activity requires only a slight increase in energy expenditure for most men in most circumstances, there is a small absolute increase in risk of an adverse cardiac event occurring during sex or within 2 hours of sexual activity.63 The Princeton Guidelines help to evaluate a man's risk for an adverse cardiac event during or shortly after sexual activity.64 These guidelines tell us that some men with active cardiac risk factors or disease fall into a high- or intermediate-risk category for adverse cardiovascular events and require further cardiac evaluation. The vast majority of men, however, fall into the low-risk category for adverse cardiovascular events with increased sexual activity and can safely be treated for ED.64

Evaluating men with erectile function for future cardiovascular risk

ED can serve as a valuable signal of the need for cardiovascular assessment, especially in men with more established coronary risk factors.55 Early recommendations are suggesting that men with ED should be screened for both heart disease risk and depression.66-68 Depression is a known risk factor for cardiovascular disease.69-71 This process could lead to early diagnosis and management. The US Preventive Services Task Force has found insufficient evidence to screen low-risk patients or patients at increased risk for the presence of cardiovascular disease using resting electrocardiography, exercise treadmill testing, or electron beam computerized tomography.76 However, clinicians should investigate men with ED for comorbid cardiovascular conditions that might then be treated at an earlier date, and these patients should be assessed for coronary heart disease risk according to recommended guidelines and algorithms.72

Many strategies have been suggested that include office-friendly measurements of endothelial dysfunction along with more traditional risk assessment to clarify which men with ED are at increased risk of cardiovascular disease.19 A reasonable approach would be to use the Framingham equation, although this equation does not yet include ED as a potential predictor of coronary artery disease.73 The assessment of cardiac risk after a complaint of erectile problems can potentially reduce subsequent morbidity and mortality. We need to determine if measures of vascular endothelial function can compete with other risk factors such as age, systolic blood pressure, serum lipid fraction levels, blood glucose levels, and insulin resistance. Some experts have suggested that men with ED are probably candidates for aggressive treatment to improve endothelial function with treatments such as statins and angiotensin converting enzyme inhibitors or angiotensin receptor blockers.74

Treatment of erectile dysfunction

Treatment plans need to be goal-oriented, ideally aimed at satisfying the needs of both the man and his partner and maximizing the chance of achieving patient satisfaction (Table 27.7). Based on the desired outcome, treatment can be simply pharmacologic or it may include further comprehensive psychosocial and relationship counseling. In many cases, the partner can be brought in to participate in the discussion about the goal of treatment, improving the chance of success.

Educational and psychosocial interventions

In most cases, regardless of etiology, the treatment options of the physiologic impairment of ED are the same (see Table 27.4). Education is the first step in treatment and is personalized to the needs of the specific patient. The normal changes of aging are often misunderstood by patients and lead to problems. Myths and misunderstandings about sexual activity can directly cause sexual difficulties as well as generate
anxiety, guilt, and worry that have a negative impact on sexual response and erectile ability (see Table 27.4). Helping men to have realistic expectations and to better understand healthy function and honest, constructive communication with partners can encourage more satisfactory sexual interaction and a healthier sense of sexual nature. Research has demonstrated that the amount of sexual intimacy correlates with relationship satisfaction.

The easily obtained erection begins to disappear in older men, especially those with chronic illness, such as diabetes, hypertension, or renal disease. Direct tactile stimulation of the penis may be needed to obtain and maintain an erection. The man becomes increasingly anxious, thereby causing further erectile difficulties. Information from the physician about these changes of aging can be extremely reassuring.

Partner issues vary widely. Issues around partner choice, partner participation in sexual activity, and partner physiology may influence erectile function. When vaginal dryness or vaginal atrophy leads to loss of lubrication and pain, women often lose interest in continued sexual activity.

### Lifestyle and medication changes

Making healthy lifestyle changes may reduce the symptoms of ED and improve general physical health. Patients need to understand what is bad for the heart is bad for the penis. Elimination of smoking tobacco is probably helpful in reducing incident ED. Dietary changes, including intake of reduced cholesterol and trans-fats, elimination of hyperglycemia when present, and decreased salt intake when salt-sensitive hypertension is noted, all help to diminish progression of vascular insufficiency. Exercise will increase cardiac output and improve peripheral circulation. A recent study of obese men with ED without diabetes, hypertension, or dyslipidemia, found that reducing caloric intake and increasing physical activity was associated with improved sexual function in about one-third. These positive changes were associated with significant improvements in erectile function, which were highly correlated with both amount of weight loss and increased activity levels. Exercise training improves endothelial function in the coronary and peripheral circulation in patients with cardiovascular disease. Programs designed to increase physical endurance clearly have a positive effect on vasculature, probably by improving endothelial function related to an increase in nitric oxide (NO) production and decreased oxidative stress, which leads to an increase in NO availability. These recommendations will help men be healthier and, it is hoped, happier, although their effect on erectile function may not be instantly apparent.

Changing medication regimens to remove causative agents can be tried when clinically possible. Examples of this might be discontinuing a thiazide diuretic and substituting an alpha-adrenergic blocker, or weaning the patient from digoxin if the medication is not necessary. Treatment of antidepressant-induced sexual dysfunction can sometimes be managed by reducing drug dosages, altering the timing of drug dosages, taking drug holidays, adding an adjunctive drug, and switching to an alternative antidepressant. These substitutions and eliminations may meet with some success, but they need to be individualized depending on clinical circumstances.

### Direct pharmacologic and surgical treatment

Specific treatment regimens for ED include oral medications, transurethral suppositories, intracavernosal injection, vacuum devices, and surgery. First-line therapies include oral medications and vacuum constriction devices. Oral treatments approved in the USA by the Food and Drugs Administration include sildenafil, tadalafil, and vardenafil. The mechanism of action, efficacy, and adverse effects of these three phosphodiesterase (PDE) type 5 inhibitors are described in other chapters in this volume. Primary care clinicians are writing about 80–85% of all the prescriptions for PDE-5 inhibitors in the USA and are usually responding positively to patients’ requests for a specific name brand.

Other pharmacologic treatments being used much less often by primary care clinicians include yohimbine and intraurethral or intracavernosal injections of vasodilating medications Apomorphine, a dopamine agonist that causes central initiation of an erection through specific action in the brain, is available in Europe but not in the USA. Vacuum devices are a reasonable choice for many men and their partners who are in a stable relationship and are willing to accept the inconvenience.

Testosterone augmentation, available as skin patches, gels, buccal patches, or injections, is best reserved for patients with documented hypogonadism based on the morning serum free testosterone level. Generally, testosterone augmentation is associated with enhanced libido. This may improve erectile status by restoring interest and perhaps through other neurohormonal mechanisms, but relying solely on testosterone to restore erectile function is inappropriate. Testosterone augmentation requires thorough evaluation and monitoring for prostate cancer.
The most common surgical treatment for ED is penile implant surgery. This is a successful therapy, but it should be reserved for patients who have considered or tried several other treatments. The surgery is irreversible and the normal function of the corpus cavernosa is obliterated.

Some clinicians have advised that ED can be managed naturally, although no controlled trials exist. A dietary program rich in whole foods including vegetables, fruits, whole grains, and legumes has been suggested, with key nutrients including zinc, essential fatty acids, vitamin A, vitamin B, L-arginine, and vitamin E. Herbal supplements such as ginseng, kava kava, and saw palmetto have also been discussed. Herbs, spices, and other foods reported to increase sexual desire include nutmeg, saffron, parsley, vanilla, avocado, carrot, and celery.

**Optimizing treatment with phosphodiesterase type 5 inhibitors**

PDE-5 inhibitors have been available for the treatment of ED since 1998. The success rates achieved for significant improvement of ED (efficacy) in rigorous scientific studies range from 60% to 80% in most populations tested, and early expectations of similar success among the general population were similarly high. Unfortunately, in real life many men with ED do not seem to be achieving their desired or expected goal with these agents. The discontinuation rate for PDE-5 inhibitor use among men diagnosed as having ED by their physicians appears to be high, even among those who initially responded to the medication, reaching up to 57% in 3-year follow-up.97,98

Discussions about appropriate expectations are the key to optimizing outcomes from PDE-5 inhibitor therapy (Table 27.8). Myths and misunderstandings about sexual activity can directly cause sexual difficulties as well as generate anxiety, guilt, and worry that have a negative impact on sexual response and erectile ability (Table 27.9).9,14,75 Men need to be told that although the medication is likely to have a positive and significant effect on erectile function in men with ED, the degree of effect can vary on the basis of a variety of physiologic and psychosocial factors. The biochemical effect of PDE-5 inhibitors does not promise 100% success in all men, and it appears to be decreased in men with diabetes or who have had a radical prostatectomy.99,100

An algorithm meant to deal with treatment failures includes re-evaluation and adjustment of therapy, with treatment for hypogonadism if present, dose titration, and patient instruction on optimal use of medication. If the man is still not satisfied, this algorithm suggests considering alternative oral or local therapy with additional education and counseling followed by referral to a specialist if needed.91

Our goal as physicians for men with ED is to:

- help to improve the man’s sexual function and self-esteem;
- improve the man’s sense of well-being; and
- improve the man’s relationships.

We know that improving physiologic erectile function in men with ED is an important part, but only one part, of the desired outcome. Many other issues can influence the likelihood of achieving the desired outcomes including:

- the man’s psychosocial milieu;
- the presence of other sexual issues or risk factors for physical sexual dysfunction;
- the availability and receptivity of a partner; and
- partner interaction.

A trusting physician–patient partnership enhances the likelihood of a successful therapeutic outcome. Optimism is an essential management tool for clinicians to use in responding to sexual issues.

**Table 27.8 Treatment failure**

<table>
<thead>
<tr>
<th>Treatment failure</th>
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<tbody>
<tr>
<td>Re-educate about appropriate goals, medication use, dose titration</td>
</tr>
<tr>
<td>Consider more detailed psychosocial problems or interventions</td>
</tr>
<tr>
<td>Consider adjunctive pharmacotherapy</td>
</tr>
<tr>
<td>Consider alternative pharmacotherapy</td>
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<tr>
<td>Refer to a specialist</td>
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</tbody>
</table>

**Table 27.9 Men’s misconceptions about ED**

<table>
<thead>
<tr>
<th>Men’s misconceptions about ED</th>
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</thead>
<tbody>
<tr>
<td>Matters relating to sexual dysfunction are taboo</td>
</tr>
<tr>
<td>Loss of erection is not a common problem, and their problem is unique</td>
</tr>
<tr>
<td>ED is a normal part of aging</td>
</tr>
<tr>
<td>ED is primarily a psychological problem and not a physical one</td>
</tr>
<tr>
<td>Treatment options are generally lacking or are too invasive and risky to be pursued</td>
</tr>
<tr>
<td>Erections are indicators of sexual desire</td>
</tr>
<tr>
<td>An erection should stay hard until ejaculation</td>
</tr>
<tr>
<td>An erection is necessary to have sexual relations</td>
</tr>
</tbody>
</table>

**Follow-up of treatment for erectile dysfunction**

Follow-up is an essential part of management of ED. Patients should be seen 1 month after initiation of treatment to evaluate progress. Comparison to baseline can be done by verbal exchange or by using the standardized questionnaire measuring erectile function (SHIM). Reviewing the success or lack of success of treatment and any adverse effects, and considering dose or treatment alterations, is more likely to achieve the patient’s goal. Further education or basic sex counseling can be provided to the patient with or without his partner.
Consultation with subspecialists

Consultation with subspecialists may be appropriate at varying intervals when managing a man with ED. The major factor is the primary care clinician’s comfort in discussing and managing treatment options. The obligation of the primary care clinician is to recognize ED and to make the patient feel comfortable about seeking help. Initial work-up and treatment can be planned by the primary care clinician who has good communication skills about sexual activity and who is knowledgeable about first-line treatments. Common indications for referral to an appropriate specialist include:

- significant penile anatomic disease;
- a younger patient with a history of pelvic or perineal trauma;
- cases requiring vascular or neurosurgical intervention;
- complicated endocrinopathies;
- complicated psychiatric or psychosocial problems; and
- patient or physician desire for further evaluation.

Urologists can be helpful in difficult or complex ED situations or when the patient presents with an anatomical problem such as Peyronie’s disease. An endocrinologist may be consulted to assist in managing men with difficult-to-control diabetes, hypogonadism, or evidence of pituitary dysfunction.

Sex therapists are practitioners in the medical or mental health field who, in addition to their basic clinical education, have had additional training in sex therapy, including evaluation and treatment options. Sex therapists have more time to talk with the patient, to work with couples and suggest enhancement techniques, and to educate couples that there are many ways of having pleasurable sexual relations without a firm erection. Such therapists could be physicians, ministers of religion, or mental health professionals. In the USA, the American Association of Sex Therapists and Counselors (http://www.aasect.org) can provide a directory for your state of trained, certified sex therapists. Most major teaching hospitals have such a trained therapist on their staff.

REFERENCES


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28 Phosphodiesterase type 5 inhibitors: molecular basis for pharmacological effects
Sharron H Francis and Jackie D Corbin

Introduction
The connection between cGMP elevation and relaxation of smooth muscle gained increased attention in the 1980s, owing largely to the work of Murad, Ignarro, and Furchgott, who demonstrated that an ‘endothelial-derived factor’ (EDRF), which was later identified as nitric oxide (NO), increased cellular cGMP and relaxed smooth muscle (Figure 28.1). Results of in vitro studies employing cyclic nucleotide analogs with known affinities for activation of cGMP-dependent protein kinase (PKG) or cAMP-dependent protein kinase (PKA) supported a prominent role for cGMP and PKG, but not PKA, in smooth muscle relaxation.1

Role of cGMP in smooth muscle relaxation
In the early 1990s, cGMP signaling was implicated in mediating penile erection. At that time, pharmacological treatments of erectile dysfunction (ED) focused largely on injections that elevated cAMP, including prostacyclins and papaverine, a relatively non-specific phosphodiesterase (PDE) inhibitor. The work of numerous laboratories established that activation of guanylyl cyclase by NO released from penile nerves and endothelium increased synthesis of intracellular cGMP.2,4 The increase in cGMP decreased the tone of smooth muscles encircling tonically constricted helicine arteries and lacunae of the penile corpus cavernosum; this permitted blood vessel diameters to expand and accommodate increased blood flow as well as increased filling of the sinuses within the penis (Figure 28.2). Vascular smooth muscle relaxation is primarily mediated by cGMP binding to PKG and activating the enzyme, which transfers the gamma-phosphate of ATP to serines or theserines (i.e. phosphorylation) in many cellular proteins. In smooth muscle these proteins include phospholamban, myosin-targeting subunit of myosin light chain phosphatase, inositol 1,4,5-triphosphate receptor-associated PKG substrate, calcium-activated potassium channels, Rho-A, PDE-5, and PKG itself via autophosphorylation.7 Phosphorylation of these proteins frequently alters their functions, many of which are involved in cellular calcium homeostasis. PKG action promotes lowering of intracellular calcium through increased calcium extrusion and increased calcium sequestration in intracellular stores, as well as desensitizing the cell to calcium signals. PDE-5, which specifically breaks down cGMP, is commonly found in high abundance in cells containing PKG and is implicated as an important down-regulator of cGMP signaling.

Selective phosphodiesterase type 5 inhibitors
Identification of potent and highly selective PDE-5 inhibitors that proved to be effective as oral medications for treatment of ED was a medical milestone (Figure 28.3).8-10 Sildenafil, developed by Pfizer, was the first of these; it set a high standard for safety and efficacy in treating ED in a diverse spectrum of patients. Vardenafil, a product of Bayer, and tadalafil, a product of ICOS–Lilly, soon joined the market and provided additional therapeutic options for effective and safe treatment of ED.11-13 Among these three medications, vardenafil is the most potent in vitro with a PDE-5 50% inhibitory concentration (IC50) of 0.1–0.4 nM compared to IC50 values of 3.5 nM and 2 nM for sildenafil and tadalafil, respectively (Figures 28.3, 28.4).14 Udenafil, a product of Dong Pharmaceuticals, was recently introduced and has an IC50 of 6 nM (see Figure 28.3).15 In 2006, sildenafil was approved under a separate formulation in the United States for use in treatment of pulmonary hypertension; the potential for use of these inhibitors in treatment of other maladies related to vascular diseases is being increasingly appreciated.16 Vardenafil, sildenafil, and tadalafil are commonly referred to as PDE-5-specific inhibitors, but PDE-5-selective inhibitors is a more accurate term.15 Owing to structural similarities among the catalytic sites of PDEs, absolute specificity of an inhibitor for one family is perhaps non-existent. Indeed, cross-reaction of vardenafil, sildenafil, and tadalafil with members of certain other PDE families has been demonstrated.17 Although the possibility of non-PDE target proteins for these medications has not been entirely excluded, evidence suggests that almost all of their known effects are mediated by their inhibition of PDE-5 activity. This includes increased
relaxation of vascular smooth muscle, which improves erectile function and causes modest hypotension in some patients. Many of the most commonly reported adverse effects (headache, facial flushing, dyspepsia, muscle aches, and stuffy or runny nose) associated with use of these medications are transitory and mostly due to vasodilatory effects in local tissues brought on by PDE-5 inhibition.\textsuperscript{37} Diarrhea, although a relatively uncommon adverse effect of these drugs, is also likely to be due to inhibition of the abundant PDE-5 catalytic activity in gastrointestinal epithelial cells and smooth muscle. Visual effects (blurred vision, perturbation of color vision, or increased light sensitivity) may be due to sildenafil or vardenaft inhibition of the PDE-6 family (retinal PDEs), which is highly similar to PDE-5. Sildenafil inhibits members of the PDE-6 family with an approximately 10-fold lower potency than for PDE-5, and vardenaft inhibits the PDE-6 family with four- to 25-fold lower potency than for PDE-5. At the highest therapeutic doses of sildenafil, the maximum free plasma concentration approaches 40 nM, a concentration that could inhibit a portion of the PDE-6 activity, but it is unlikely to block other PDEs. For example, potency of sildenafil inhibition of the PDE-1 family is approximately 80-fold weaker than for PDE-5 and, at the maximum free plasma concentration achieved in most patients, it would be predicted to have little effect.\textsuperscript{37}

A few studies have reported that PDE-5-selective inhibitors possess neural effects. Halen et al. reported that vardenaft, sildenafil, and tadalafil blunted release of NO from neurons in rabbit isolated corpus cavernosal tissue.\textsuperscript{18} It was suggested that this could be protective against excessive smooth muscle relaxation leading to priapism; whether this effect is mediated via inhibition of neuronal PDE-5 and cGMP elevation is unclear. Reports of PDE-5-selective inhibitor effects on the central nervous system were initially met with skepticism because the inhibitors were not believed to cross the blood–brain barrier, and it was conjectured that improved blood flow to certain brain regions could account for the results. However, reports of such effects on central nerves continue to accumulate in studies using both animal models and humans. Zhang et al. demonstrated that sildenafil or tadalafil administration in rats improves recovery from stroke, an effect that could be due to improved blood flow; however, sildenafil also improves survival of neuronal cells in culture.\textsuperscript{19} Improved object recognition memory and memory consolidation following administration of PDE-selective inhibitors were reported.\textsuperscript{20} Results of studies in hamsters indicated that sildenafil is effective in rapid adjustment of the circadian clock.\textsuperscript{21} The mechanism or mechanisms mediating these processes is not known.

Tadalafil has low affinity for most PDEs other than PDE-5, but it cross-reacts appreciably with the PDE-11 family, which is also highly similar to PDE-5 in amino acid sequence.\textsuperscript{22} Tadalafil potency among PDE-11 isoenzymes (PDE-11-A1, -A2, -A3, and -A4) differs by approximately 5-fold, so that selectivity of tadalafil for PDE-5 versus PDE-11 varies 8- to 40-fold.\textsuperscript{23} No effects that are clearly attributable to cross-reaction between tadalafil and PDE-11 have been described, but the physiological role of PDE-11 is unknown. The apparent absence of a clinical effect of tadalafil on PDE-11 may be due to the apparently restricted expression and low mammalian
Molecular characteristics of phosphodiesterase type 5

PDE-5 tissue distribution is relatively restricted; this, along with the high potency of the inhibitors in clinical use, may contribute to the low incidence of side-effects. PDE-5 is most abundant in smooth muscle, platelets, gastrointestinal epithelial cells, and Purkinje cells. It is present in certain endothelial cells and at low levels in cardiomyocytes. Since PDE-5 is particularly abundant in vascular smooth muscle, all PDE-5-selective inhibitors are likely to reduce vascular tone. The three PDE-5 isoenzymes (PDE-5-A1, -A2, and -A3) are alternative mRNA spliced products of a single gene; they differ in amino acid sequence only near the amino terminus, and significant enzymatic differences among them have not been detected.

In most tissues, PDE-5 is largely cytosolic. It is composed of two tightly associated proteins of approximately 98kDa (Figure 28.5), each of which contains an amino-terminal regulatory (R) domain and a carboxyl-terminal catalytic (C) domain. PDE-5 contains two types of sites that interact with cGMP with high specificity:

- a catalytic site where cGMP is hydrolyzed to inactive 5'-GMP; and
- allosteric sites that are provided by one of the GAF sub-domains in the R domain.
as PKG and the PDE-5 catalytic site for binding cGMP.\textsuperscript{31} While bound to the allosteric sites, cGMP cannot be hydrolyzed; this would sequester and preserve cGMP, thereby rapidly lowering the cellular free (‘active’) cGMP level; as cytosolic cGMP declines, it could provide a reservoir for slow release of cGMP.\textsuperscript{32}

**Mechanism by which inhibitors block phosphodiesterase type 5 catalytic activity**

PDE-5 inhibitors that are currently in use for treatment of ED are small molecules that contain bicyclic ring structures that mimic the guanine ring of cGMP (see Figure 28.3). Each competes directly with cGMP for access to the PDE-5 catalytic site, thus inhibiting the enzyme (see Figure 28.5). These inhibitors do not interact with the allosteric cGMP-binding sites in the R domain; nor do they bind to other known cGMP-binding proteins. This is due to the fact that the cGMP-binding sites in the PDE-5 R domain, the PDE-5 C domain, and the catabolite-gene activator (CAP)-related sites in PKG or the cGMP-gated ion channels are evolutionarily and biochemically distinct.\textsuperscript{33} The rigorous specificity of the PDE-5 allosteric cGMP-binding sites may aid in the development of new medications that regulate PDE-5 through these sites.

PDE-5 inhibitors, whether potent or weak, and cGMP are believed to utilize some of the same amino-acid contacts in the catalytic site of PDE-5; however, some of the contacts with potent inhibitors could be stronger than those made by cGMP, and potent inhibitors are thought to make many more contacts than does cGMP. This is likely to account for the 1000- to 40,000-fold higher affinity of these molecules for the PDE-5 catalytic site. The contacts between the PDE-5 catalytic site and cGMP are unknown because the co-crystal structure of cGMP with PDE-5 has not yet been determined.

The X-ray crystal structures of the PDE-5 C domain in complex with vardenafil, sildenafil, or tadalafil reveal that each makes several kinds of amino-acid contacts with PDE-5 (Figure 28.6).\textsuperscript{33,34} These include hydrogen bonds, hydrophobic interactions, salt bridges, and van der Waals forces. As expected, in the PDE-5 catalytic site each inhibitor contacts amino acids that are conserved in other PDEs and contribute importantly to inhibitor potency. Insights derived from the crystal structures were used as a guide for site-directed mutagenesis of PDE-5 to quantify the importance of these contacts for potency and selectivity of the inhibitors. These include an invariant glutamine (Gln-817) involved in hydrogen bonding, and a hydrophobic pocket that includes a conserved phenylalanine (Phe-820), an invariant tyrosine (Tyr-612), and a cluster of other hydrophobic residues (Ala-767, Val-782, Ala-783, Phe-786, and Leu-804). Vardenafil and sildenafil form a water-bridge with zinc (see Figure 28.6), one of the metals that participate in hydrolysis of the cyclic phosphate ring; tadalafil, which has potency similar to that of sildenafil, does not make this contact. In addition to forming contacts that are conserved in the PDE superfamily, each inhibitor also makes novel contacts with amino acids that are closely apposed to, but are not within, the catalytic site. These involve amino acids.
Influence of regions outside the phosphodiesterase type 5 catalytic site on inhibitor potencies and selectivities

Although the inhibitors form most of their contacts within or very near the PDE-5 catalytic site, the R domain can influence potency and selectivity of the various inhibitors. The isolated PDE-5 C domain and full-length PDE-5 have similar affinities for cGMP as substrate, and the catalytic rates ($k_{\text{cat}}$) are similar indicating that the salient features of enzyme function are not altered by removal of the R domain. The potency ($IC_{50}$) of sildenafil for these two enzyme forms is similar, and this also applies to the potency of tadalafil. However, the higher potency and selectivity of vardenafil over sildenafil or tadalafil for PDE-5 inhibition requires the R domain, i.e. the potencies of the three inhibitors are essentially the same in its absence (Table 28.1). This diminished affinity for vardenafil could involve loss of direct contacts between the R domain and vardenafil, or it could be due to a conformational influence of the R domain on the catalytic site; no evidence has yet been found for direct contacts between the R domain and vardenafil. The results emphasize that caution should be used in extrapolating characteristics established with one compound (e.g. sildenafil) to another group of compounds such as vardenafil-based molecules.

Regulation of substrate affinity and catalytic activity by allosteric cGMP binding or phosphorylation

An agonist-induced increase in cGMP in smooth muscle cells such as those in the penile corpus cavernosum activates a negative feedback mechanism that increases cGMP hydrolysis, and cGMP is quickly lowered to basal or near-basal levels. This feedback is a classical mechanism for maintaining the concentration of a signaling ligand in a range that is optimal for cellular responsiveness to the signal – that is, it protects the cell from excessive accumulation of cGMP following a signal from an agonist such as NO.

PDE-5 mediates negative feedback in the cGMP pathway as follows. Upon elevation of cellular cGMP, the rate of cGMP breakdown by PDE-5 increases significantly since the catalytic site of the enzyme is not fully occupied by cGMP; this increase
in catalytic rate is strictly a process of mass action due to substrate elevation. Cyclic GMP association with allosteric sites in the R domain also occurs, and increases both the affinity and the hydrolytic rate of the catalytic site for cGMP. Increased occupation of the catalytic and allosteric sites with cGMP elicits a conformational change in the PDE-5 R domain that exposes Ser-102 in human PDE-5 for phosphorylation by cyclic nucleotide-dependent protein kinases. Ser-102 is preferentially phosphorylated by PKG, which would also be activated when intracellular cGMP increases. Phospho-PDE-5 exhibits increased affinity for cGMP at the allosteric sites as well as the catalytic site and fosters increased cGMP breakdown. These mechanisms act in concert to lower cGMP levels quickly (Table 28.2). Negative feedback on the cGMP pathway is also observed by increased sequestration of cGMP in the PDE-5 allosteric sites, which blocks activation of PKG by cGMP.

### Regulation of phosphodiesterase type 5 affinity for inhibitors by allosteric cGMP binding or phosphorylation

Natural mechanisms that provide for negative feedback regulation of cellular cGMP also regulate PDE-5 affinity for inhibitors. cGMP binding to allosteric sites in the R domain produces a conformational change in PDE-5 that increases affinity of the catalytic site for vardenafil, sildenafil, or tadalafil by approximately three-fold; thus, as cellular cGMP increases as a result of inhibitor effects to block cGMP hydrolysis, more cGMP is available to occupy the allosteric sites, which enhances catalytic site affinity for the inhibitors. This type of effect is referred to as ‘feed-forward regulation’. In this case mechanisms that physiologically provide for negative feedback regulation enhance the pharmacological efficacy of the medications. Phosphorylation of Ser-102 in the human PDE-5 R domain also increases affinity of the catalytic site for tadalafil and perhaps for vardenafil and sildenafil as well. It is likely that allosteric cGMP binding and phosphorylation of Ser-102 occur simultaneously and work in concert to promote greater potency of the inhibitors. The effects of phosphorylation on PDE-5 affinity for inhibitors should be reversed by the action of phosphoprotein phosphatases such as phosphoprotein phosphatase-1, which has been shown to dephosphorylate PDE-5 efficiently in vitro as well as in intact cells.

### Phosphodiesterase type 5 inhibitors promote their own potencies

PDE-5 exhibits two components of affinity (high affinity and low affinity) for vardenafil, sildenafil, and tadalafil. The basis
for these kinetic states is not certain, but their combined influence is reflected in inhibitor potency (IC$_{50}$). Recent studies demonstrated that after 12 hours of exposure of PDE-5 to a medically relevant level of tadalafil or vardenafil, the low-affinity state was converted into the high-affinity state for the respective inhibitors (Blount M, unpublished data). This would be predicted to increase the potency of these inhibitors. The increased affinity of PDE-5 for inhibitors is associated with an apparent elongation of the protein, which is presumed to be the more optimal conformer for enzymatic function.

Mechanisms of phosphodiesterase type 5 that may contribute to long-lasting effects of inhibitors

Several studies documented that relief of ED following use of PDE-5-selective inhibitors persists well beyond the half-life for plasma clearance. The molecular mechanism that provides for this effect is not known. The conversion of PDE-5 to a conformation with higher affinity described above may contribute to these long-lasting effects increased affinity induced by a conformational change in PDE-5 would be predicted to lower the concentration required to block enzyme activity and to foster rebinding of the inhibitor to PDE-5 upon its dissociation. Repeated rebinding of inhibitor to PDE-5 would slow its exit from the cell and sustain the pharmacological effects for a longer period than predicted from the plasma clearance profile. Likewise, allosteric cGMP binding and/or phosphorylation of PDE-5 following elevation of cGMP (or both) would improve PDE-5 affinity for inhibitors and translate into slowed decline of the inhibitor and its effects in the cell. Lastly, the exact mechanism whereby elevation of cGMP and activation ofPKG relaxes penile vascular smooth muscle is poorly understood; these effects may persist well after clearance of the inhibitors from the cell.

The level of PDE-5 in smooth muscle cells of the corpus cavernosum in combination with its high affinity for the inhibitors may also have an impact on the persistence of the effect of these medications. One can consider sildenafil as an example. The free level of sildenafil in plasma (i.e. sildenafil not bound to serum albumin) following ingestion of the medication is about 40 nM and the level of PDE-5 holoenzyme in the corpus cavernosum is about 95 nM. Assuming that free inhibitor in the plasma fully equilibrates with the cytosol, only half of the PDE-5 would be inhibited and perhaps this degree of inhibition is sufficient for the pharmacological effects. However, given the high affinity of PDE-5 for the inhibitors, it is predicted that inhibitor entering the cell would be immediately bound so that the level of the inhibitor that is free in the cytosol would be very low (<4 nM), but eventually almost all of the PDE-5 catalytic sites would be filled. At that time, it is predicted that the concentration of free inhibitor in the cytosol and the plasma would equalize, but the total amount of inhibitor in the cell (at concentrations of 95 nM bound to PDE-5 plus 40 nM free in the cytosol, making a total of 135 nM) would be greater than that of free inhibitor (40 nM) in an equal volume of plasma. As plasma inhibitor declines, unbound inhibitor in the cytosol would be predicted to decline in parallel. However, the decline in the inhibitor bound to PDE-5 is likely to be substantially slower, owing to both the high affinity of PDE-5 for the inhibitor and to the rapid and repeated rebinding of inhibitor that dissociates from the enzyme. In this scenario, the high concentration of cellular PDE-5 would provide more opportunities for rebinding of inhibitor to PDE-5 prior to its exit from the cell.

Conclusion

PDE-5-selective inhibitors such as vardenafil, sildenafil, and tadalafil have proven to be highly effective in treatment of ED. The basic features of PDE-5 structure provide for regulation of the catalytic site of this enzyme, including modulation of catalysis as well as affinity for these inhibitors.

Acknowledgments

Supported by NIH DK40299 and DK58277.

REFERENCES

Introduction

Apart from corpus cavernosum, phosphodiesterase (PDE) type-5 isozyme is expressed in various other tissues, including the arterial and venous vasculature, the skeletal visceral and tracheobronchial muscles, the brain, the retina, and platelets. The differential distribution of PDE-5 isozyme in various tissues, as well as the different selectivity of the pharmacologic agents, forms the basis for potential tissue-specific effects of PDE-5 inhibitors. Accumulation of data in this context has delineated the overall profile of actions of PDE-5 inhibitors, has expanded indications of use to include idiopathic pulmonary hypertension (specifically for sildenafil), and even shows potential for further therapeutic applications. It should be stressed, however, that although the three currently available agents show many similar modes of actions, an effect proven for one agent does not necessarily apply to the others. Furthermore, extrapolations of experimental evidence to the clinical setting should be made with caution.

Effects on cardiac function and coronary circulation

The cardiovascular effects of PDE-5 inhibitors are summarized in Table 29.1.

Myocardium

Direct analysis of effects on cardiac function has been obtained in vitro, but these results remain limited and conflicting. PDE-5 gene expression is present in human heart, although protein expression and enzyme activity have been questioned. Recent evidence has shown that although gene and protein expression is indeed low, PDE-5 is compartmentalized within the myocyte and its inhibition can alter cardiac function. This is not observed under resting conditions, but only when the heart is stimulated (e.g. by adrenergic agonists or pressure overload). Indeed, there is evidence that PDE-5 inhibition by sildenafil can blunt the systolic responses to beta-adrenergic stimulation and deactivate multiple hypertrophy signaling pathways triggered by pressure load (Figure 29.1). These findings support a possible role of the drug in modifying stimulated cardiac function and reducing myocardial hypertrophy. A significant upregulation of PDE-5 isozyme and an inotropic effect due to acute PDE-5 inhibition has been reported recently in hypertrophied human and animal right ventricular models.

Coronary vasculature

Patients with coronary artery disease exhibit reduced basal activity of nitric oxide (NO) in the atherosclerotic epicardial and microvascular coronary circulation. Since PDE-5 isozyme is expressed in coronary arteries, its inhibition has been hypothesized to augment coronary blood flow. Studies with sildenafil in dogs and humans confirmed modest flow increases in normal and diseased coronary arteries. Tadalafil improved myocardial blood flow during periods of increased workload in both normal and poorly perfused regions of myocardium. Sildenafil administration may augment coronary blood flow by improving aortic stiffness and by reducing amplitude and delaying arrival of wave reflections from peripheral sites.

Cardioprotective effects

Ischemic preconditioning is a powerful cardioprotective phenomenon according to which recurrent episodes of ischemia protect against future myocardial infarction and stunning. A significant number of experimental studies have shown that PDE-5 inhibitors have a preconditioning-like cardio protective effect against ischemia and reperfusion injury (see Figure 29.1). While the increase in cGMP levels (with activation of protein kinase G and subsequent opening of the mitochondrial K_ATP channels) by PDE-5 inhibitors is suspected to be the most likely mechanism of protection, an additional signaling cascade that may be triggered concurrently includes increased expression of endothelial NO synthase (eNOS) and inducible NO synthase (iNOS); activation of extracellular signal-regulated kinase and protein kinase C (PKC); and opening of the mitochondrial K_ATP channels.
### Table 29.1 Cardiovascular effects of phosphodiesterase type 5 inhibitors

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pathophysiological mechanisms</th>
<th>Clinical implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardium</td>
<td>Suppression of beta-adrenergic or pressure overload stimulated systolic function</td>
<td>Benefit in disorders in which neurohormonal stimulation is enhanced such as hypertension, left ventricular hypertrophy, and heart failure</td>
</tr>
<tr>
<td>Coronary vasculature</td>
<td>Epicardial coronary vasodilation, increase coronary blood flow</td>
<td>Favorable effects in patients with vasospastic angina or diffuse coronary microvessel disease</td>
</tr>
<tr>
<td>Preconditioning-like cardioprotection</td>
<td>Opening of the mitochondrial K&lt;sub&gt;ATP&lt;/sub&gt; channels due to increased cGMP levels with activation of protein kinase G, increased expression of eNOS and iNOS, activation of ERK and protein kinase C</td>
<td>Preconditioning-like cardio protective effect against ischemia/reperfusion injury, potential use in coronary artery bypass surgery</td>
</tr>
<tr>
<td>Cardiac repolarization</td>
<td>None of the three agents are dangerously associated with QTc prolongation. Mild prolongation with vardenafil</td>
<td>Precautions for use in patients with congenital QT prolongation and with class IA and class III antiarrhythmics (vardenafil)</td>
</tr>
<tr>
<td>Blood pressure and heart rate</td>
<td>Mild lowering of blood pressure and clinically insignificant heart rate changes</td>
<td>To be further evaluated as potential antihypertensive agents in essential hypertension</td>
</tr>
<tr>
<td>Pulmonary vasculature</td>
<td>Targeting of the NO/cGMP pathway Reduction of plasma levels of endothelin-1 Inhibition of the hypoxia induced cytokine expression (TNF-alpha, IL-1-beta)</td>
<td>Sildenafil has been approved for the treatment of idiopathic pulmonary arterial hypertension. Beneficial effects in pulmonary arterial hypertension, either idiopathic or associated with congestive heart failure, connective tissue disease or with repaired congenital systemic-pulmonary shunts or sickle cell disease</td>
</tr>
<tr>
<td>Peripheral vascular structure and function</td>
<td>Reversal of endothelial dysfunction Decrease of aortic stiffness and wave reflections</td>
<td>Favorable effects in patients with heart failure, coronary artery disease, or hypertension, and in patients with increased cardiovascular risk. Symptomatic relief of patients with Raynaud’s phenomenon</td>
</tr>
<tr>
<td>Systemic effects (anti-oxidative stress – inflammation)</td>
<td>Potent inhibition of superoxide formation Reduction of inflammatory markers and mediators</td>
<td>Beneficial effects in patients with risk factors and increased oxidative stress and subclinical inflammatory state</td>
</tr>
<tr>
<td>Platelets</td>
<td>Increased threshold for activation of the platelet glycoprotein Ilb-Ilia receptor</td>
<td>Potential adjunctive use as anti-platelets agents in patients with coronary artery disease. Potential benefit in Raynaud’s phenomenon and sickle cell disease</td>
</tr>
<tr>
<td>Neurological recovery</td>
<td>Regulation of angiogenesis and neurogenesis, as well as synaptic plasticity, after stroke</td>
<td>Possible neurological functional recovery after embolic stroke (experimental studies)</td>
</tr>
</tbody>
</table>

ERK, extracellular signal-regulated kinase; QT<sub>c</sub>, corrected QT interval; NO, nitric oxide; TNF, tumor necrosis factor; IL, interleukin

### Cardiac repolarization

Cardiac electrophysiology effects of PDE-5 inhibitors, especially as manifested by changes in the QT interval, have been studied. None of the three agents is dangerously associated with prolongation of the corrected QT interval, although vardenafil has a warning of use for patients with congenital QT prolongation and for patients using class IA and III antiarrhythmics. Patients with heart failure, however, constitute a group that warrants further investigation.

### Effects on blood pressure and heart rate

All PDE-5 inhibitors produce rather small changes in systolic and diastolic blood pressure in both the supine and standing condition after a single-dose administration. There is no clear dose–response relationship. In healthy subjects, changes are of the following magnitude: sildenafil 100 mg decreases blood pressure by 3.7/3.6 mmHg for systolic and diastolic pressure, respectively; vardenafil 20 mg decreases blood pressure by 7.5/8 mmHg; and tadalafil 20 mg decreases blood pressure by 1.6/0.8 mmHg. Greater declines in blood pressure may be observed in treated and untreated hypertensive patients. In patients with severe coronary artery disease, sildenafil showed small (<10%) but significant decreases in systemic arterial pressures. Similar effects on central and peripheral hemodynamic parameters in patients with coronary artery disease have also been reported for tadalafil and vardenafil.

Blood pressure effects are consistent with arteriolar effects of PDE-5 inhibitors on the peripheral vasculature as a result of an increase in cGMP in vascular smooth muscle. Dilatation of the brachial artery extends even to patients with refractory hypertension. Of interest is the finding that
sildenafil exerts a stimulatory effect on renin secretion. Thus, the resultant increase in the activation of the renin–angiotensin system could counteract the vasodilation and this could partly account for the rather small net effects on blood pressure by PDE-5 inhibitors.18

Heart rate changes compensatory to blood pressure reduction have either not been shown or are clinically insignificant.8,16

**Effects on pulmonary vasculature**

PDE-5 isoenzyme is widely expressed in pulmonary vascular smooth muscle and in newly muscularized distal pulmonary arterioles, and it is thought to limit the vasodilator and anti-proliferative cGMP-mediated effects of vasoactive factors such as NO and the natriuretic peptides.19 Enhanced PDE-5 activity in response to chronic hypoxia has been implicated in the pathophysiology of pulmonary hypertension. Thus, PDE-5 isoenzyme is an attractive target for the pharmacologic manipulation of pulmonary vascular function and structure. Indeed, PDE-5 inhibitors cause relaxation of pulmonary vascular smooth muscles by activating large-conductance, calcium-activated potassium channels.20 Reduction of plasma levels of endothelin-1 may also account for pulmonary vasorelaxation effects.21 Recent experimental studies showed that tadalafil, but not sildenafil or vardenafil, inhibited hypoxic pulmonary vasoconstriction through attenuation of hypoxia-induced pulmonary artery cytokine expression.22

The effects of PDE-5 inhibitors in pulmonary hypertension are shown in Figure 29.2.

**Effects on the peripheral vasculature**

**Endothelial function**

Endothelial dysfunction is the key event in the pathophysiology of erectile dysfunction (ED), and men with penile vascular dysfunction have endothelial dysfunction in other vascular beds as well. ED and generalized vascular disease may be linked at the level of the endothelium with a defective NO–cGMP system being a common abnormality.23

There are data suggesting that PDE-5 inhibitors might be of use in reversing generalized endothelial dysfunction (Figure 29.3). Acute or mid-term sildenafil treatment showed favorable effects on brachial artery flow-mediated dilatation up to 24 hours after dosing in men with and without ED24–26 and in patients with coronary artery disease2 and chronic heart failure.27,28 Moreover, mid-term therapy with tadalafil led to a significant sustained improvement of endothelial function in patients with increased cardiovascular risk regardless of their degree of ED.29 Vardenafil restored impaired endothelial function of cavernous and brachial arteries.30

ED patients with or without cardiovascular risk factors exhibit reduced endothelial progenitor cells. Tadalafil (chronically, in ED patients) and vardenafil (acutely, in healthy subjects and ED patients) increased the number of circulating endothelial progenitor cells, suggesting an intriguing role of these drugs in the mobilization or production of endothelial progenitor cells that promote endothelial rehabilitation.31

**Arterial stiffness and wave reflections**

Large artery stiffness and arterial wave reflections are important determinants of left ventricular function, coronary blood flow, and the mechanical integrity of arteries. They are involved in the pathogenesis of systolic hypertension and they have been identified as independent markers and prognosticators of cardiovascular risk. Carotid–femoral pulse wave velocity and wave reflections indices decreased after acute sildenafil administration (Figure 29.4).10,32,33 Studies regarding mid-term administration have showed favorable (Vlahopoulos C et al., unpublished data) and neutral effects.34

**Systemic effects**

**Oxidative stress**

Oxidative stress is implicated in endothelial damage and increased destruction of NO. In vitro studies showed that
increased production of reactive oxygen species is associated with impaired erectile response, owing primarily to reduction of NO concentrations. The inhibitory action of the NO–cGMP axis on NAD(P)H oxidase expression mediated by PDE-5 inhibition may contribute to a potent inhibition of superoxide formation.\textsuperscript{14}

Subclinical inflammation
ED adds an incremental inflammatory and endothelial–prothrombotic activation on top of coronary artery disease and, interestingly, equivalence between ED and coronary artery disease in terms of endothelial or inflammatory activation has been shown.\textsuperscript{35,36} There is evidence that PDE-5 inhibitors have a beneficial effect on inflammatory activation. A 12-week antioxidant treatment (propionyl l-carnitine) plus sildenafil reduced monocyte activation and markers of endothelial damage [intracellular adhesion molecule (ICAM)-1, P-selectin] and penile vascular damage (end-diastolic velocity) in patients with diabetic ED.\textsuperscript{37} Furthermore, a 4-week administration of sildenafil\textsuperscript{26} and tadalafil\textsuperscript{18} showed a favorable effect on endothelium-dependent vasodilatation of cavernous arteries in men with ED that was accompanied by a favorable effect on markers of endothelial function and inflammation, including adhesion molecules (VCAM and ICAM), endothelin-1, and highly sensitive C-reactive protein (hsCRP), and IL-6, as well as on insulin. Given the unfavorable effect of inflammation on arterial function,\textsuperscript{39} the beneficial effect of PDE-5 inhibitors on the latter\textsuperscript{18,24,30,32,33} could be partly attributed to an anti-inflammatory action of the drug, and, indeed, this is further supported by preliminary data from our laboratory (Vlachopoulos C et al., unpublished data).

Platelets
Sildenafil increases the threshold for activation of the platelet glycoprotein IIb–IIIa receptor without an effect on platelet degranulation.\textsuperscript{7} This is consistent with potentiation of the anti-aggregatory action of NO donors by sildenafil.\textsuperscript{7} It has also been suggested that sildenafil may have a biphasic effect on platelets, consisting of an initial transient stimulatory response that promotes platelet aggregation and a subsequent inhibitory response that limits thrombus size.\textsuperscript{3} Whether the observed anti-platelet effect results in a clinically relevant benefit requires further investigation.

Neurological recovery
Cyclic nucleotides (cGMP and cAMP) may play a critical role in modulating brain function under physiological and pathological conditions by affecting angiogenesis, neurogenesis, and synaptic plasticity. Sildenafil and tadalafil improved neurological functional recovery and selectively increased cerebral blood flow level in the ischemic boundary when administered in rat models after embolic stroke. Improved functional recovery was associated with upregulation of brain cGMP levels.\textsuperscript{40}
Phosphodiesterase type 5 inhibitors and disease states

Coronary artery disease

PDE-5 inhibitors are widely used as a primary pharmacological treatment of ED in men with and without (known) underlying cardiovascular disease. Although initial reports of adverse cardiac events were reported soon after approval of sildenafil, a compelling body of data suggests that PDE-5 inhibitors do not significantly increase the risk of non-fatal myocardial infarction, stroke, or cardiovascular deaths. Sildenafil, especially, has been extensively studied. A review of numerous clinical trials indicates this drug generally has a good safety profile in men with ED and concomitant cardiovascular disease and its administration is not associated with ischemic events, either at the time of introduction of treatment or during longer-term use. Even in patients with severe coronary artery disease, sildenafil does not affect coronary artery diameter and basal flow, while it increases coronary flow reserve.

Favorable modes of action of PDE-5 inhibitors include improvement of vascular function and an ischemic preconditioning-like effect. Based on these properties, they could be potentially used as cardiovascular drugs in patients with vasospastic angina or diffuse coronary microvessel disease and in patients undergoing coronary artery bypass grafting. Furthermore, although their potency is modest compared with other agents that specifically target platelet adhesion and aggregation, their adjunctive use as anti-platelet agent could be also considered.

Despite their safe profile, PDE-5 inhibitors should not be used in patients at high risk, including those with unstable angina, recent myocardial infarction (<2 weeks), on life-threatening ventricular arrhythmias. NO donors in combination with PDE-5 inhibitors cause a profound and unpredictable decline in blood pressure and are contraindicated. Despite some studies showing the dissipation of the interaction effect before 24 hours, to date, the 24-hour period between nitrate use and short-acting PDE-5 inhibitor administration (up to 48 hours for the long-acting tadalafil) appears prudent until...
Figure 29.4 Effects of phosphodiesterase type 5 inhibitors on aortic stiffness (PWV, pulse wave velocity) and wave reflections (Alx, augmentation index). (a) Patients with coronary artery disease (CAD). (b) Patients with heart failure (HF). (c) Patients with arteriogenic erectile dysfunction (ED) and increased cardiovascular risk. Adapted with permission from Vasc Med 2003; 8: 243–8,18 and Am J Cardiol 2005; 96: 1436–40,22 and from Vlachopoulos C (unpublished data).

additional data, including information on outliers and patients with coronary artery disease, are available.41

Heart failure

Patients with heart failure have an increased prevalence of ED, and sildenafil has been shown to be safe and effective for the treatment of ED in patients with symptomatic heart failure (New York Heart Association classes II and III).19,44 The efficacy of sildenafil in the treatment of pulmonary arterial hypertension has prompted investigation of a potential utility of PDE-5 inhibition in the treatment of heart failure patients with secondary pulmonary hypertension (see below). Sildenafil improves cardiac performance and exercise capacity in heart failure patients; mechanisms include improvement of endothelial function and reduction of large artery stiffness and wave reflections.27,28,32,45,46 This agent protects the alveolar-capillary membrane in chronic heart failure patients both at rest and during sub-maximal exercise. It improves tissue oxygenation during exercise and gas diffusion at the lung level, and it protects the alveoli from exercise-induced edema formation.47 Interesting experimental data suggest direct myocardial effects of PDE-5 inhibition that may counteract beta-adrenergic, hypertrophic, and pro-apoptotic signaling, three critical pathways in the development of left ventricle dysfunction.2 Prophylactic treatment with sildenafil prevented apoptosis and left ventricular dysfunction in a chronic model of doxorubicin-induced cardiomyopathy.48

Experimental and clinical myocardial effects of sildenafil are shown in Figure 29.5.

Systemic hypertension

Data from multiple trials support safety of use of PDE-5 inhibitors in hypertensive men with ED being treated with monotherapy or a multidrug antihypertensive regimen.15 PDE-5 inhibitors did not increase the incidence of adverse events or hypotensive episodes. Although PDE-5 inhibitors are no longer contraindicated with alpha-blockers, all three PDE-5 inhibitors carry precautions regarding the use of alpha-blockers, owing to the possible development of orthostatic hypotension with concomitant use. Thus, administration and dosing should be according to the most recent package insert.41

Although the acute blood pressure-lowering effect in treated hypertensive patients is modest, the potential of PDE-5 inhibitors as antihypertensive agents has also been explored. Active mid-term treatment with sildenafil reduces ambulatory and clinic blood pressure by an extent similar to that observed with the other classes of antihypertensive drugs.33 In an acute study, an incremental antihypertensive effect of a single dose of tadalafil has been demonstrated in uncontrolled hypertensive subjects on multiple agents.49 However, at this stage, the use of PDE-5 inhibitors as antihypertensive agents cannot be advocated.

Pulmonary hypertension

Sildenafil has been shown to be beneficial in patients with pulmonary arterial hypertension (Figure 29.6), either idiopathic or associated with heart failure, connective tissue
Phosphodiesterase type 5 inhibitors: non-erectile dysfunction cardiovascular effects

Figure 29.5  Experimental and clinical myocardial effects of sildenafil. (a) Prevention and reversal of myocardial hypertrophy and failure induced by pressure load. (b) Increase in cardiac index due to afterload reduction in systolic heart failure. Adapted with permission from Nat Med 2005; 11: 214–22, and Am J Cardiol 2005; 96: 1436–40.

Figure 29.6 Improvement of hemodynamics and functional capacity by sildenafil in pulmonary hypertension. (a) Magnetic resonance imaging angiography shows reversal of the pathological septal shift after sildenafil treatment. (b) Change from baseline to 12 weeks in the distance walked in 6 minutes. This distance increased from baseline in all sildenafil groups; the mean placebo-corrected treatment effects were 45 m (+13.0%), 46 m (+13.3%), and 50 m (+14.7%) sildenafil for 20 mg, 40 mg, and 80 mg, respectively (p<0.001 for all comparisons). Adapted with permission from Circulation 2003; 108: 2066–9, and N Engl J Med 2003; 353: 2148–57.

disease, or repaired congenital systemic–pulmonary shunts. It significantly improves exercise capacity by improving pulmonary hemodynamics and reducing right ventricular afterload. It also reduces right ventricular mass, as determined by magnetic resonance imaging. It is well tolerated and, on the basis of recent clinical studies, it has been approved at a dose of 20 mg three times daily for improving exercise tolerance in patients with idiopathic pulmonary hypertension. It should be stressed, however, that despite their common classification as PDE-5 inhibitors, all three agents are not equally efficacious in the treatment of pulmonary hypertension (Table 29.2). While a reduction in mean pulmonary artery pressure, in pulmonary–systemic vascular resistance ratio, and in right ventricle afterload, as well as an increase in cardiac index, has been reported with all three PDE-5 inhibitors, only sildenafil caused a significant improvement in arterial oxygenation. The cause of these differences between the agents is not known, but one possibility is the different selectivities of the three PDE-5 inhibitors with respect to other PDE isoforms. These agents may also differ in their binding capacity to PDE-5 during hypoxia.

Congenital heart disease

Increased pulmonary vascular resistance complicating congenital heart disease may be caused by a dysfunction in endogenous pulmonary endothelial NO production. In patients with Eisenmenger’s syndrome, sildenafil improves not only hemodynamic parameters but symptomatic status and exercise capacity as well. Improvement of pulmonary blood flow is of the same magnitude as in patients with idiopathic pulmonary hypertension. Preliminary evaluation of tadalafil has shown beneficial effects of this agent on hemodynamics, tolerability, and efficacy over a 12-week period. In patients with large atrial septal defects, sildenafil improves pulmonary arterial hemodynamics and right ventricular function and relieves symptoms associated with severe pulmonary arterial hypertension.

Connective tissue diseases

Secondary pulmonary hypertension
Pulmonary arterial hypertension is a frequent complication of connective tissue diseases. Recent studies suggest that sildenafil
can be used as a pulmonary vasodilator in systemic sclerosis patients with secondary pulmonary hypertension. Sildenafil also reduces pulmonary artery pressure and increases quality of life in patients with systemic lupus erythematosus.\textsuperscript{24}

Raynaud’s phenomenon

Impaired endothelial-dependent vasodilation is implicated in Raynaud’s phenomenon, in which digital ischemia results from vasoconstriction of the digital arteries, pre-capillary arterioles, and cutaneous arteriovenous shunts. Available evidence suggests that sildenafil and vardenafil, through their vasoactive and platelet-inhibitory effects, may lead to improved microcirculation, symptomatic relief and ulcer healing in patients with vasodilator-resistant Raynaud’s phenomenon.\textsuperscript{35} Limited data suggest similar effects with tadalafil.

Sickle cell disease

Increased endothelial cell activation is involved in the pathophysiology of sickle cell disease. In addition, pulmonary hypertension is increasingly recognized as a complication of sickle cell disease, with a prevalence of approximately 30%. In patients with sickle cell disease and mild–moderate pulmonary hypertension, chronic therapy with sildenafil reduced pulmonary arterial systolic pressure and improved exercise capacity.\textsuperscript{36} Administration of sildenafil also potentiates reduction of platelet activation through NO-dependent signaling.\textsuperscript{5} These findings support a role of PDE-5 inhibitors for counteracting vascular dysfunction and impaired thrombotic state in such patients.

Table 29.2 PDE-5 inhibition in patients with pulmonary hypertension: pulmonary hemodynamic effects and functional changes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sildenafil</th>
<th>Tadalafil</th>
<th>Vardenafil</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPAP</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>No difference in the magnitude of response among the drugs</td>
</tr>
<tr>
<td>PVR/SVR</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>Vardenafil lacks pulmonary selectivity</td>
</tr>
<tr>
<td>Cardiac index</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>No difference in the magnitude of response among the drugs</td>
</tr>
<tr>
<td>Alveolar gas exchange</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>Sildenafil exerts a favorable effect on ventilation–perfusion matching</td>
</tr>
<tr>
<td>RV hypertrophy</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>During chronic hypoxia, sildenafil normalizes RVSP and reduces right ventricle hypertrophy; the other agents not tested</td>
</tr>
<tr>
<td>Exercise capacity</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>Improvement in pulmonary hemodynamics and reduction in right ventricular afterload; trials with the other agents under way</td>
</tr>
</tbody>
</table>

PDE, phosphodiesterase; mPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance index; RV, right ventricle; RVSP, right ventricle systolic pressure; SVR, systemic vascular resistance index

Conclusion

A substantial body of studies shows that PDE-5 inhibitors have a wide multitude of actions on the cardiovascular system. These actions carry significance in two directions. First, and most important, they support the safety of this class of agents. Second, they show potential for indications beyond the primary approval of these drugs. At present, sildenafil is the only agent that has such an additional indication, namely idiopathic pulmonary hypertension. Further data are needed to assess the additional clinical benefit of this very promising class of agents.

REFERENCES

1. Wallis RM, Corbin JD, Francis SH, Ellis P. Tissue distribution of phosphodiesterase families and the effect of sildenafil on tissue cyclic nucleotides, platelet function, and the contractile responses of trabecular carnea and aortic rings in vitro. Am J Cardiol 1999; 83: 3C–12C.
51. Ghofrani HA, Voswinckel R, Reichenberger F, et al. Differences in hemodynamic and oxygenation responses to three different


Sildenafil: first in the therapeutic class of phosphodiesterase type 5 inhibitors

Culley C Carson III

Introduction

The introduction of oral agents for the treatment of erectile dysfunction (ED) has revolutionized the treatment of men with erection problems of all severities and etiologies. Sildenafil, available on the world market since 1998, was joined in 2003 by tadalafl and vardenafil as effective and reliable oral agents for the treatment of ED. While these agents have the same mechanism of action, there are differences among the three agents. Sildenafil has the longest patient experience and the most robust data confirming its activity, safety, and tolerability. It has recently been released for use in pulmonary hypertension as well as ED.

Among the earliest recognized phosphodiesterase (PDE) inhibitors were caffeine and theophylline. The first PDE inhibitor used clinically for the treatment of ED was papaverine, a non-selective inhibitor of PDE-5. Papaverine is administered via injection into the corpora cavernosa of the penis, either alone or in combination with other vasoactive agents. Sildenafil, the first oral PDE-5 inhibitor, was approved for use in men with ED in 1998. The addition of vardenafil and tadalafl to the market has increased the number of approved PDE-5 inhibitors to three agents used throughout the world. Each of these agents has a similar mechanism of action, but there are pharmacological and clinical differences. The molecular structures of sildenafil, vardenafil, tadalafl, and cGMP are shown in Figure 30.1.

All three approved agents in this class have similar pharmacokinetic and pharmacodynamic profiles and each is effective for all ages of patients with ED of all severities and etiologies. While there are clear pharmacokinetic and pharmacodynamic differences amongst these agents, clinical differences are somewhat more difficult to identify. Indeed the data of preference trials, head-to-head clinical trials, and selection trials are few. The differences in pharmacokinetics, while having distinct advantages in marketing each drug, may be difficult for clinicians and patients to identify. With the lack of data and good-quality clinical trials, it is difficult for the clinician to differentiate among the three agents and to select a PDE-5 inhibitor for a specific ED patient or a specific agent to switch to if an initial PDE-5 agent is unsuccessful or poorly tolerated.

Pharmacokinetics

Specificity

One classification of differences amongst the three PDE-5 inhibitors is that of specificity for phosphodiesterase inhibition. Because the PDE enzyme is a participant in erectile function, inhibition is a method of facilitating erectile function. cGMP facilitates the relaxation of smooth muscle cells in the corpus cavernosum through the nitric oxide (NO) pathway. Because PDE-5 in the corpus cavernosum smooth muscle cells breaks down cGMP, inhibition or blockade of this enzyme will prolong the duration and increase the concentration of cGMP in the smooth muscle cell, facilitating erectile function. Currently 11 families of PDEs have been identified in the human. Selectivity of the three currently available PDE-5 agents is predominantly for PDE-5; however, there is some additional inhibition of other PDE enzymes by the various agents (Table 30.1). Sildenafil has excellent selectivity for PDE-5 over all the other PDEs except for PDE-6, which has some degree of inhibition from both sildenafil and vardenafil, most significantly sildenafil. This selectivity for PDE-6 produces a dose-related impairment of blue-green color discrimination and leads to the blue vision that some patients report. This PDE-6 inhibition is not related to the blindness caused by non-arteritic ischemic optic neuropathy reported with some PDE-5 agents.

Absorption and metabolism

Because of differences in gastrointestinal absorption with fatty meals and time of absorption, the three drugs have differences in ultimate peak plasma concentrations based on food intake. Sildenafil, when taken with a high-fat meal, has a reduction in maximum concentration (Cmax) of approximately 29%, with delays in time to peak plasma concentration (Tmax) that can be as long as 1 hour. This interaction may result in delayed onset or reduced efficacy because of a decrease in peak serum concentration. This reduction may result in treatment failure in some patients. Thus, patients taking sildenafil should be instructed to do so either 1–2 hours after eating or with a reduced fat meal.
The cytochrome P (CYP) 450 system is the chief metabolic pathway for sildenafil, which is a CYP3A4 substrate. Similarly, sildenafil has a desmethyl metabolite that accounts for approximately 20% of its overall pharmacologic activity. Sildenafil has a terminal half-life of approximately 4–5 hours. Excretion is principally as fecal metabolites, with 80% of oral doses excreted in the feces. In men ages 65 years or older, the area under the curve (AUC, i.e., the systemic exposure) of sildenafil increases by 40%. Therefore, lower starting doses are recommended for the elderly, beginning at 25 mg with dose escalation as required by patient response and side-effects.

### Duration of action

The three available PDE-5 inhibitors have some significant differences in serum half-life. Sildenafil has a half-life of 4 hours, but it may be clinically active for as long as 8 hours because of prolonged adherence to receptor sites beyond the usual serum half-life. The clinician must be aware that emergency treatment with nitrate medications following ingestion of sildenafil should be delayed for 24 hours.

### Onset of action

Multiple studies have been performed to evaluate the onset of activity of the three PDE-5 inhibitors. Because of the artificial nature of these studies, clinical relevance continues to be controversial. Onset of action studies are designed to use stopwatch evaluations by patients or partners following ingestion of the PDE-5 agent. Significance in onset of action is measured as first measurement of statistically significant difference in erectile function compared with placebo. While this statistically significant difference may occur as early as 11 minutes with sildenafil, success at this early time occurs for fewer than 40% of patients treated. In patients with significant risk factors and comorbidities for ED, counseling to begin sexual activity at 15 minutes or earlier leads to treatment failure and may, in the final analysis, create performance anxiety, and patients may inappropriately lose confidence in the treatment.

### Drug interactions

Use of any PDE-5 inhibitor agent is absolutely contraindicated in patients taking any form of nitric acid (NO) donor, especially organic nitrates. Sildenafil can potentiate the vasodilator and hypotensive effects of these agents. Reductions in blood pressure with nitrates have been observed within 24 hours after taking sildenafil; therefore, nitrates should not be used to manage acute myocardial ischemia in a patient who has taken sildenafil within the prior 24 hours.

Acute postural hypotensive symptoms have also been observed when sildenafil is administered together with the alpha-adrenergic blocker doxazosin, which is indicated for

---

**Table 30.1 PDE-5 inhibitors: selectivity for PDE-5 versus other PDE isoenzymes**

<table>
<thead>
<tr>
<th>PDE Isoenzyme</th>
<th>Sildenafil</th>
<th>Tadalafil</th>
<th>Vardenafil</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDE-1</td>
<td>80</td>
<td>&gt;4000</td>
<td>690</td>
</tr>
<tr>
<td>PDE-2</td>
<td>&gt;19,000</td>
<td>&gt;4000</td>
<td>62,000</td>
</tr>
<tr>
<td>PDE-3</td>
<td>4628</td>
<td>&gt;4000</td>
<td>40,000</td>
</tr>
<tr>
<td>PDE-4</td>
<td>2057</td>
<td>&gt;4000</td>
<td>47,000</td>
</tr>
<tr>
<td>PDE-6 (rod)</td>
<td>11</td>
<td>188</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>(cone)</td>
<td>10</td>
<td>153</td>
</tr>
<tr>
<td>PDE-7</td>
<td>6100</td>
<td>&gt;14,000</td>
<td>&gt;300,000</td>
</tr>
<tr>
<td>PDE-8</td>
<td>8500</td>
<td>&gt;14,000</td>
<td>&gt;300,000</td>
</tr>
<tr>
<td>PDE-9</td>
<td>750</td>
<td>&gt;14,000</td>
<td>5800</td>
</tr>
<tr>
<td>PDE-10</td>
<td>2800</td>
<td>&gt;14,000</td>
<td>30,000</td>
</tr>
<tr>
<td>PDE-11†</td>
<td>780</td>
<td>6</td>
<td>1620</td>
</tr>
</tbody>
</table>

*Selectivity ratio for phosphodiesterase (PDE) type 5=1 for all inhibitors; higher ratios indicate lower selectivity.
†Physiological role and clinical relevance are not yet known.

---

**Figure 30.1** Molecular structure of three marketed phosphodiesterase type 5 inhibitors and their molecular similarity to cGMP.
the treatment of benign prostatic hyperplasia as well as hypertension. Sildenafil at doses exceeding 25 mg should not be administered within 4 hours of a patient taking an alpha-blocker. 

Concomitant administration of sildenafil with other anti-hypertensive agents (e.g. calcium-channel blockers) does not result in significant declines in blood pressure or in increased occurrence of hypotension, syncope, or other adverse cardiovascular events compared with placebo. 

Alcohol is a mild vasodilator with effects on NO synthase activity and NO output by endothelial cells. In a placebo-controlled crossover trial involving eight healthy non-smoking men, there were no untoward hemodynamic interactions between sildenafil 100 mg and red wine (750 ml, 13.5% v/v) consumed 60 minutes after sildenafil dosing (i.e. time of peak plasma concentration for sildenafil). Red wine intake significantly elevated cardiac index and heart rate, and sildenafil alone significantly lowered mean arterial pressure by up to 7% and peripheral vascular resistance by up to 8%. However, the combination had no effect on any of these parameters compared with red wine alone.

Potent CYP3A4 inhibitors, including HIV protease inhibitors (e.g. indinavir, ritonavir),azole antifungals, and macrolide antibiotics (e.g. erythromycin, azithromycin) can increase systemic exposure (the AUC) of sildenafil by two- to 16-fold. Conversely, CYP3A4 inducers such as rifampin can reduce circulating PDE-5 inhibitor levels.

Grapefruit juice inhibits first-pass CYP metabolism in the gastrointestinal tract and may thus increase oral bioavailability of the PDE-5 inhibitors. A randomized crossover trial evaluated the effects of taking a single sildenafil 50 mg dose 1 hour before, or at the same time as, 250 ml of grapefruit juice in 24 healthy male volunteers. Compared with water (reference period), grapefruit juice consumption increased the AUC values for sildenafil and N-desmethylsildenafil by about 23–24% and slightly prolonged the time to peak plasma concentration (by about 15 minutes). Grapefruit juice also rendered sildenafil pharmacokinetics more variable, and the authors concluded that the combination should be avoided, especially in patients who might be prone to more marked hemodynamic effects.

### Adverse events

Most adverse events (AEs) associated with sildenafil therapy are caused by inhibition of PDE-5 in tissues other than the corpus cavernosum (see Table 30.2). Sildenafil-associated AEs occur in ≥3% of patients and include:

- headache in 16% of patients taking sildenafil compared with 4% of men receiving placebo;
- flushing (10% vs 1%);
- dyspepsia (7% vs 2%); and
- nasal congestion (4% vs 2%).

Discontinuations because of AEs were infrequent, occurring in 2.5% of patients receiving sildenafil compared with 2.3% of patients receiving placebo. AEs appear to decline over time in published studies of sildenafil.

<table>
<thead>
<tr>
<th>Table 30.2 Adverse events with phosphodiesterase type 5 inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse event</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Flushing</td>
</tr>
<tr>
<td>Nasopharyngitis, rhinitis, or nasal congestion</td>
</tr>
<tr>
<td>Dyspepsia</td>
</tr>
<tr>
<td>Abnormal vision</td>
</tr>
<tr>
<td>Sinusitis</td>
</tr>
<tr>
<td>Flu syndrome</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Myalgia</td>
</tr>
</tbody>
</table>

### Safety

Extensive treatment of patients with vascular risk factors using sildenafil has demonstrated safety in cardiac patients. Indeed, sildenafil was originally designed as a cardioprotective agent, and clinical and laboratory studies have confirmed this safety. The Princeton Consensus Guideline Conference II carefully reviewed the risks, AEs, and safety of PDE-5 inhibitors in men with cardiac disease. This expert conference, with meta-analysis of available phase III studies, demonstrated no increased risk of cardiac events in patients taking PDE-5 inhibitors compared with placebo-treated patients or patients in the general, age-adjusted population with similar age and risk factor profiles. Indeed, in several of the studies reviewed, patients taking regular PDE-5 inhibitors were demonstrated to have fewer cardiac events than those not taking PDE-5 inhibitors.

While clinical trials of sildenafil have included large numbers of patients with cardiovascular disease and diabetes mellitus, they have excluded patients with unstable cardiovascular disease. Accordingly, PDE-5 inhibitors are either not recommended or are to be used with caution in men with unstable angina, recent myocardial infarction, cardiac failure, a life-threatening or uncontrolled arrhythmia, poorly controlled blood pressure (resting blood pressure less than 90/50 mmHg or more than 170/100–110 mmHg), or heart failure. In addition, patients with left ventricular outflow obstruction secondary to aortic stenosis or idiopathic hypertrophic subaortic stenosis, as well as men with severe autonomic insufficiency, may be especially sensitive to the vasodilator effects of PDE-5 inhibitors. Consensus guidelines have been issued for risk-stratifying and counseling patients with concomitant sexual dysfunction and cardiovascular disease. Men with ED and associated significant cardiovascular conditions must be counseled that there is a transient increase in the relative risk of cardiovascular events during and within about 2 hours.
after sexual intercourse with or without PDE-5 inhibitor treatment. Exercise echocardiographic studies have demonstrated that treatment with sildenafil 50–100 mg did not adversely affect hemodynamic variables, exercise capacity (treadmill time), or time to cardiac ischemia (or first awareness of angina) in patients with stable coronary artery disease.

In clinical trials of sildenafil, the incidence rate of myocardial infarction ranged from 1.0 per 100 patient-years for patients taking sildenafil in open-label studies to 1.7 per 100 patient-years for those receiving sildenafil in randomized controlled trials, as against 1.4 per 100 patient-years for those randomized to placebo in such trials. The slight disparities between incidence rates of myocardial infarction across sildenafil trials may reflect differences in age or other patient characteristics at baseline.

Even at supratherapeutic doses consistent with concomitant treatment with CYP inhibitors or renal impairment, sildenafil does not increase the corrected QT interval in a clinically significant manner. Sildenafil 50–400 mg does not increase the absolute QT interval, and elicited only mild rises in the Fridericia-corrected QT interval duration 1 hour after dosing in healthy adult males ages 45–60 years (mean, 53) who also received the active control moxifloxacin. These findings, together with the absence of reports of torsades de pointes in sildenafil post-marketing surveillance databases, suggest that none of the PDE-5 inhibitors causes clinically significant prolongation of the QT interval.

Case reports have implicated PDE-5 inhibitors in non-arteritic ischemic optic neuropathy (NAION), a rare form of acute blindness usually found in elderly patients with significant vascular risk factors. While fewer than 50 cases have been reported in the world literature, multiple clinical, epidemiologic, and basic science studies have been completed to examine the link between PDE-5 inhibitors and blindness. This association is not related to the blue-tinted vision reported by some sildenafil patients. This latter finding is transient and related to the inhibition of PDE-6 in the cones of the eye. Animal studies of the optic nerve after sildenafil demonstrate increased optic nerve blood flow, opposite to the expected finding with non-arteritic ischemic optic neuropathy. Similarly, an estimate of the frequency of cases in a non-treated population shows similar numbers of cases to that reported in association with PDE-5 use, with no signal to increased prevalence.

The systemic exposures of sildenafil may be increased in patients with renal insufficiency or hepatic impairment. Starting or other doses may need to be limited to sildenafil 25 mg in patients with these conditions.

**Clinical effectiveness data**

The US Food and Drug Administration approved sildenafil in March 1998 after extensive clinical trials. Because sildenafil has an almost 10-year history of safety and efficacy, it has more extensive clinical and laboratory data to demonstrate its use in varied etiologies, populations, and severities of ED. Early data for sildenafil include a 12-week randomized, placebo-controlled study of sildenafil 50 mg that demonstrated 65% of successful intercourse attempts compared with 20% in a placebo group. In reviewing these studies, however, it is clear that 25–35% of patients in these clinical study protocols had inadequate responses to PDE-5 inhibitors. Sildenafil phase 3 trials were reported in the *New England Journal of Medicine* in 1998. In a dose-escalation (50–100 mg) study involving 329 men (mean age, 59 years) with ED for about 5 years (organic ED in 55% or more of cases), the mean score for the erectile function domain of the International Index of Erectile Function (IIEF) at the end of 12 weeks of treatment was 22.1 (mild) in the sildenafil group compared with 12.2 (moderate) in the placebo group (p<0.001). Scores on the orgasmic function, intercourse satisfaction, and overall satisfaction domains (but not the sexual desire domain) also significantly improved.

**Long-term efficacy**

With the increasing experience of PDE-5 inhibitor treatment for ED, efficacy over time is becoming better documented. Long-term studies including 5- and 6-year data from sildenafil have demonstrated no clinical evidence for tachyphylaxis. Indeed, the long-standing efficacy of sildenafil, the agent longest on the market, strongly suggests that this class of agents continues to be effective with long-term use. Since these agents are used only on an as-needed basis, few patients have taken daily doses for long periods of time. The few long-term daily dosing studies, however, have not demonstrated conclusively any evidence for tolerability or tachyphylaxis. Similarly, daily dosing studies, while still limited in duration, show improved, not compromised, responses in comparison with on-demand dosing.

**Difficult-to-treat patients**

All three PDE-5 inhibitors have been demonstrated to be effective in patients with severe erectile dysfunction. Indeed, patients with prostate cancer who have had radiation therapy or radical surgery and patients with severe vascular disease, diabetes, or depression are all treated satisfactorily with these agents. While the efficacy declines in these patients with severe erectile dysfunction, these agents are safe and effective, but consideration in these patients should be given to increasing dosage levels to maximum acceptable dose.

Men with diabetes mellitus are at elevated ED risk and are difficult to treat. Sildenafil has been demonstrated as effective therapy for men with diabetic ED. The Sildenafil Diabetes Study Group reported that 56% of men with diabetic ED who received sildenafil (25–100 mg) treatment for 12 weeks reported improved erections, in contrast to 10% of patients receiving placebo (p<0.001). In this study, 61% of men randomized to sildenafil reported at least one successful attempt at sexual intercourse compared with 22% of controls (p<0.001).

Because intact innervation to the penis is necessary for physiologic erectile responses, substantial proportions of patients with prostate cancer experience ED following either nerve-sparing radical retropubic prostatectomy or radiation therapy. Prostate cancer patients treated with sildenafil have shown significant improvements in erectile function.
open-label sildenafil study involving 84 men (mean age, 62 years) with ED 2.1 years post-prostatectomy, 53% of patients receiving treatment at doses of 50–100 mg reported improved erections, and 40% reported an enhanced ability to achieve and maintain erections. Erectile function was directly related to the degree of nerve sparing, with patients having had a bilateral nerve-sparing procedure tending to respond better than those having had a unilateral or non-nerve-sparing procedure.\textsuperscript{22} Lower pathological stage and older patient age were also predictive of improved outcomes.

Using a single question form the Erectile Dysfunction Inventory of Treatment Satisfaction rather than the entire instrument, Hong et al. documented a sildenafil treatment satisfaction rate of only 26% between 0 and 6 months after nerve-sparing radical retropubic prostatectomy, which rose to a maximum of 60% between the 18th and 24th postoperative month.\textsuperscript{23}

**Failure of phosphodiesterase type 5 inhibitor therapy**

Because as many as 30–40% of patients will not respond to PDE-5 inhibitors alone, strategies must be considered to enhance responses. Most importantly, patients must be counseled in the proper administration of PDE-5 inhibitors.\textsuperscript{24} For sildenafil, patients should be counseled to avoid high-fat meals, and patients with significant comorbidities should be advised to delay sexual stimulation for 1 hour following administration.\textsuperscript{25} Similarly, patients should be counseled that sexual stimulation is necessary. Dose escalation is also critical in achieving therapeutic success. The majority of men in marketing studies have optimal doses of 100 mg. Studies with sildenafil have demonstrated an improvement in response after patients have taken sildenafil six or more times. Because many patients have had prolonged ED, they should be counseled that multiple doses may be necessary before optimum response is achieved.\textsuperscript{4} Patients who continue to be poorly responsive to PDE-5 inhibitors should be further evaluated for hypogonadism. Indeed, sildenafil has been demonstrated to function poorly in the presence of low testosterone levels. Normalizing testosterone with testosterone gel therapy and maximizing the sildenafil dose to 100 mg will increase responses substantially. Indeed Shabsigh et al. showed improvement in erectile function domain scores of the IIEF of 4.4 points in patients treated with testosterone and sildenafil, compared with sildenafil 2.1 points with testosterone and placebo, a statistically significant difference. Additionally, those patients treated with the combination therapy had an improvement in ejaculatory function.\textsuperscript{25} Doses of sildenafil above the recommended 100 mg may be effective in some men in whom standard doses fail. McMahon showed a 24% success rate using 200 mg after previous sildenafil failures. Drop-outs were 31% and side-effects increased in all categories.\textsuperscript{26}

**Future directions**

PDE-5 inhibitors were introduced in an effort to improve erectile function. Their efficacy and safety have been well recorded in millions of patients worldwide. These agents, however, should not be confined to the treatment of ED. Early data support the improvement of endothelial cell-mediated flow in peripheral arteries via the NO pathways, suggesting a possible use for these agents as treatment for conditions known to limit endothelial function. Sildenafil is approved in the USA and in Europe for the treatment of pulmonary hypertension. Trials have confirmed the improved pulmonary dynamics with sildenafil, which appears to be more effective than standard treatment, with improvements in lifestyle and functional status.\textsuperscript{35–39}

In addition, data have demonstrated the efficacy of chronic dosing of PDE-5 inhibitors in patients following radical prostatectomy. Rehabilitation using sildenafil was demonstrated to improve post-radical prostatectomy erectile function by seven-fold in a study performed by Padma-Nathan et al.\textsuperscript{40}

**Conclusion**

Sildenafil is an effective and safe PDE-5 inhibitor, and the clinician now has multiple choices in treatment of patients with erectile dysfunction of all severities and etiologies. Since no well-controlled, head-to-head selection or patient preference studies are available, each clinician must choose an agent based on the profile of the patient, his tolerance, risk factors, and side-effects. Patients in whom activity is limited because of cardiac disease should be evaluated before PDE-5 inhibitors are prescribed, and no PDE-5 inhibitor should be prescribed in patients taking nitrate medications.

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**REFERENCES**


Introduction

Oral phosphodiesterase (PDE) type 5 inhibitors are the first-line treatment of erectile dysfunction (ED) for most patients. Owing to its efficacy, safety, ease of use, and unique pharmacological properties, tadalafil is preferred by many men suffering from ED of varying etiologies and severity. In this chapter, pharmacokinetic and updated clinical data from integrated analyses and postmarketing surveillance are reviewed, including efficacy results for specific subpopulations, an evidence-based review of on-demand, daily and chronic-dosing regimens, and compiled safety data.

Pharmacological profile

Although sildenafil, vardenafil, and tadalafil share a common mechanism of action through inhibition of PDE-5 in the corpora cavernosa and the resulting decrease in breakdown of cGMP, their chemical structures and pharmacological properties are distinct. These differences directly influence onset and duration of efficacy, resulting in unique profiles for each agent. Clinically evident differences are dependent upon pharmacokinetic parameters including maximum drug concentration, time to peak concentration, minimal effective concentration, and duration of efficacy (the time at which active drug concentration is greater than the minimum effective concentration).6

Pharmacologic parameters

The pharmacokinetic characteristics for tadalafil have been determined both in healthy men and in those with erectile dysfunction. Key studies include an integrated analysis performed on 13 clinical pharmacology studies in healthy subjects designed to elucidate the distribution characteristics for tadalafil 20 mg, a recent consolidated review of all peer-reviewed reports, and published abstracts and regulatory filings related to the pharmacology of tadalafil (Table 31.1).6-8

Tadalafil is rapidly absorbed following oral administration, with a median time to maximum serum concentration of 2 hours, compared with sildenafil (1 hour and 1.2 hours for 50 mg and 100 mg doses, respectively)6,10-12 and vardenafil (0.7 hours and 0.9 hours for 20 mg and 10 mg doses, respectively).13,14

Recent clinical reports have quantified the time to onset of clinical effectiveness for tadalafil. The time to penile rigidity firm enough for sexual activity after a 20 mg dose has been reported at 16 minutes in one-third of men, with more than 50% of men achieving increased penile rigidity sufficient for penetrative sexual activity at 30 minutes.15 Plasma concentrations of tadalafil reach 77% of maximum concentration by 1 hour after dosing. The time interval until most patients are able to complete intercourse successfully is reported as 20 minutes for sildenafil 100 mg,16 approximately 25 minutes for vardenafil 20 mg,17 and 30 minutes for tadalafil 20 mg;15 cohorts for these at-home studies (n=223–732) included men with mild to severe ED and, with the exception of vardenafil, lower doses were associated with longer onset times.6,13-18 For example, statistically significant differences for tadalafil 10 mg were observed at 45 minutes.19

The serum half-life for tadalafil is 17.5 hours,6,20,21 compared with approximately 3.8 hours for sildenafil6,22,23 and 4.2 hours for vardenafil.6,13,21 The difference in half-life is the most significant pharmacologic characteristic differentiating these three agents. Plasma concentrations of tadalafil reach 77% of maximum concentration by 1 hour after dosing, and efficacy has been established for up to 36 hours, when plasma concentrations drop to more than three-fold less than the maximum.20,25

Metabolism and excretion

Tadalafil is metabolized primarily via the cytochrome P450 3A4 (CYP3A4) pathway in the liver, and at therapeutic doses tadalafil does not induce or inhibit CYP3A4 activity. The major metabolite of tadalafil is methylcatechol glucuronide, which is more than 10,000-fold less potent as a PDE-5 inhibitor and does not contribute significantly to PDE-5 inhibitor activity.6,20,25

Effects of extrinsic and intrinsic factors on pharmacokinetics

Extrinsic factors such as food and alcohol were not shown to alter the rate and extent of absorption of tadalafil in healthy subjects.21 This important characteristic also distinguishes tadalafil from sildenafil and vardenafil. High-fat meals (with 57% of calories from fat) delay the time to maximum concentration of sildenafil by 60 minutes and reduce the maximum
Table 31.1 Pharmacokinetic parameters of phosphodiesterase 5 inhibitors

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n=74)</th>
<th>Tadalafil treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 mg (n=74)</td>
<td>20 mg (n=75)</td>
</tr>
<tr>
<td>Age (years) mean±SD</td>
<td>58.8±10.8</td>
<td>57.6±10.9</td>
</tr>
<tr>
<td>Weight (kg) mean±SD</td>
<td>91.2±17.1</td>
<td>93.6±16.7</td>
</tr>
<tr>
<td>Ethnicity, N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African descent</td>
<td>5 (6.8)</td>
<td>4 (5.4)</td>
</tr>
<tr>
<td>Western Asian</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Caucasian</td>
<td>64 (86.5)</td>
<td>68 (91.9)</td>
</tr>
<tr>
<td>East or South-east Asian</td>
<td>3 (4.1)</td>
<td>0</td>
</tr>
<tr>
<td>Hispanic</td>
<td>2 (2.7)</td>
<td>2 (2.7)</td>
</tr>
<tr>
<td>Erectile dysfunction history, N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥3 months and &lt;6 months</td>
<td>1 (1.4)</td>
<td>3 (4.1)</td>
</tr>
<tr>
<td>≥6 months and &lt;1 year</td>
<td>4 (5.4)</td>
<td>5 (6.8)</td>
</tr>
<tr>
<td>≥1 year</td>
<td>69 (93.2)</td>
<td>66 (89.2)</td>
</tr>
<tr>
<td>IIEF erectile function domain score, N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild (22–25)</td>
<td>9 (12.2)</td>
<td>10 (13.5)</td>
</tr>
<tr>
<td>Moderate (11–21)</td>
<td>39 (52.7)</td>
<td>39 (52.7)</td>
</tr>
<tr>
<td>Severe (6–10)</td>
<td>26 (35.1)</td>
<td>25 (33.8)</td>
</tr>
<tr>
<td>Comorbid conditions</td>
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<tr>
<td>Hypertension</td>
<td>35 (47.3)</td>
<td>24 (32.4)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>17 (23.0)</td>
<td>20 (27.0)</td>
</tr>
<tr>
<td>Depression</td>
<td>5 (6.8)</td>
<td>5 (6.8)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>7 (9.5)</td>
<td>3 (4.1)</td>
</tr>
<tr>
<td>Prior use of sildenafil citrate</td>
<td>7 (9.5)</td>
<td>7 (9.5)</td>
</tr>
</tbody>
</table>


concentration by 29% compared with fasting, while median time to maximum concentration for vardenafil is prolonged by 1 hour.\(^{23,24,26}\) Moderate-fat meals (with 30% of calories from fat) do not reduce either of these parameters for vardenafil.\(^{26}\)

Similarly, patient factors such as diabetes and renal impairment did not cause clinically significant changes in tadalafil pharmacokinetics. In a review of 227 patients with mild-to-severe ED, systemic exposure to tadalafil was not influenced by age, weight, smoking status, alcohol consumption, liver enzyme status, ED severity, cardiovascular condition, or diabetes mellitus.\(^{27}\) Time of administration (morning versus evening) has also not been shown to affect systemic distribution.\(^{27}\) These characteristics may translate into enhanced convenience and increased patient- and partner-reported satisfaction with tadalafil, since there is a reduced need to plan sexual activity around dosing, meals, or alcohol consumption.

### Selectivity for phosphodiesterases

Tadalafil, vardenafil, and sildenafil are all highly selective PDE-5 inhibitors. Each has a unique and distinct profile of selectivity relative to the other 10 PDEs; this aspect of pharmacology is clinically important because selectivity and predicted side-effect profiles are related. To date, at least 11 PDE families have been identified in tissues, including the heart, brain, liver, skeletal muscle, and blood vessels; PDE-5 is the dominant isozyme in the corpora cavernosa smooth muscle but it is also found in the lung, kidney, vascular and visceral smooth muscle, and platelets.\(^{28}\)

Comparisons of PDE-5 inhibition with other PDE families demonstrate in vitro specificity for PDE-5 versus PDE-6 (responsible for color vision disturbance, including a transient blue–green aura and discrimination difficulties) as follows: tadalafil is 780 times more selective for PDE-5, in comparison to 2.9 for vardenafil and 6.8 for sildenafil. Slight variability in these ratios has been reported in the literature, owing to the timing of studies or the type of assays utilized by different laboratories. Although in vitro selectivity ratios are limited by the fact that direct extrapolation to clinical findings is not possible, visual disturbances have been shown to occur in 11% of sildenafil patients,\(^{4,29}\) a small minority of those using vardenafil,\(^{4}\) and approximately 0.1% of tadalafil users.\(^{30}\)

On the other hand, the selectivity profiles for vardenafil and sildenafil in relation to PDE-11, a recently described PDE family identified in vivo from the prostate, testes, heart, and pituitary and muscle tissue, are favored in comparison with that of tadalafil.\(^{31}\) The clinical implications of this potential inhibition remain unknown, although there is evidence to suggest a role for PDE-11 in male reproduction.\(^{31,32}\) Two randomized double-blind, placebo-controlled, parallel-group
studies involving 421 men examined the effects on spermatogenesis of placebo versus tadalafil at 10mg or 20mg administered daily for 6 months (two complete human spermatogenesis cycles); on the basis of semen profiles, no adverse effects were noted. In the same study, serum levels of testosterone, luteinizing hormone, and follicle stimulating hormone were examined, with no significant changes to serum endocrine profiles in the 393 men completing this portion of the study.33

On-demand use

Tadalafil has been approved for the treatment of ED in more than 100 countries, with more than 10 million patients treated worldwide since its initial European Union approval in 2002. Tadalafil has been studied in over 100 clinical trials involving over 12,000 men, with more than 10,000 additional patients involved in ongoing studies.

Efficacy: integrated analyses

Efficacy and safety data for tadalafil were pooled from five phase 3 multicenter, fixed-dose, parallel-group trials enrolling a total of 1112 patients in 74 centers.3 Integrated analysis of these results was facilitated by common elements of study design, including inclusion and exclusion criteria; at baseline, the study population resembled that of the Massachusetts Male Aging Study (MMAS) with a mean patient age of 59,24 and nearly 60% of the men were identified as having moderate-to-severe ED of varying etiologies. Common comorbidities included hypertension (30%), diabetes (21%), and coronary artery disease (8%).3 After a 4-week treatment-free lead-in period, during which at least four attempts at sexual intercourse occurred, patients were randomized to placebo or tadalafil doses of 2.5–20 mg at a maximum of one dose per day. All studies were conducted on an intent-to-treat basis and were analyzed over a 12-week period using outcome measures that included the International Index of Erectile Function (IIEF), the Sexual Encounter Profile (SEP) diary, and a global assessment question (GAQ). Co-primary efficacy variables were defined as the change from baseline in the IIEF erectile function domain questions and SEP questions 2 and 3.3 No restrictions were placed on food and alcohol intake or timing of sexual activity.

At all doses, a statistically significant improvement from baseline erectile function was observed for tadalafil compared with placebo regardless of baseline ED etiology, severity, or patient age (Figures 31.1, 31.2, 31.3, 31.4). Almost 75% of intercourse attempts were successfully completed with 20 mg tadalafil versus 32% with placebo (p < 0.001); treatment effects were dose-dependent, with 35%, 50%, 67%, and 81% of patients (placebo, tadalafil 5 mg, 10 mg, and 20 mg, respectively) reporting improved erections (GAQ, p < 0.001). Clinically, erectile function was normalized (as defined by an IIEF score > 26) in 59% of men at a 20 mg dose compared with 11% for placebo.3

Several updates on the efficacy and safety of on-demand tadalafil have been reported, including cohorts comprising older men and those with multiple comorbidities.30–38 Carson et al. reported that an analysis of integrated data from 11 trials comprising 2102 men and limiting tadalafil doses to either 10 mg or 20 mg demonstrated mean IIEF erectile function domain score increases of 6.5 and 8.6 points, respectively,
compared with less than 1 point with placebo.28,30 Tadalafil 20 mg improved erections in 84% of men versus 33% for placebo, 50% reported improved satisfaction with erectile hardness as measured by SEP question 4 (placebo 11%), and the mean success rate for intercourse attempts (SEP question 3) was 68% for tadalafil, compared with 33% for the placebo group (p < 0.001 for all outcomes).30 Parallel improvements in patient and partner satisfaction for tadalafil compared with placebo as measured by the Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) were also demonstrated.35 Cumulatively, large-scale, randomized, multicenter, double-blind placebo-controlled trials and post-marketing surveillance have demonstrated that tadalafil is efficacious in improving erectile function across ED etiologies and severity. At a dose of 20 mg, rates of successful intercourse approach 70–75%, with return to normal erectile function in more than half of patients.

**Efficacy in diabetes**

Diabetes mellitus increases the risk of ED three-fold through vascular disease, autonomic neuropathy, and endothelial dysfunction, with as many as 75% of diabetic men affected by ED during their lifetime.36–41 More that 50% of men develop ED within 10 years of diabetes onset, and an earlier age of onset of ED in this population is frequently observed.42–45

Significant improvements for diabetic men treated with tadalafil for ED were observed for all outcome measures on the integrated analyses previously discussed.4,30 Additionally, diabetes-specific trials support these findings. Saenz de Tejada et al. reported upon the efficacy and safety of tadalafil in a randomized, multicenter, double-blind, placebo-controlled trial of 191 diabetic men (average duration of diabetes, 11.7 years) with ED, patients randomly assigned to once-daily treatment with placebo or tadalafil 10 mg or 20 mg and no restrictions for administration with respect to alcohol and food.44 Mean age and baseline ED severity were similar across groups; 90.7% of men were type 2 diabetics, and satisfactory glyemic control (defined as a glycosylated hemoglobin of <7%) was identified in only 18.5% of patients.44 Erectile function improved irrespective of diabetic type, the presence of microvascular complications, or the type of diabetic treatment. Specifically, the proportion of men reporting the ability to attain an erection (SEP question 2) was 22.2% and 22.6% for tadalafil 10 mg and 20 mg, respectively, versus a 4.1% decline for the non-treated group over the study period.44 In response to the GAQ question, 56% and 64% of men taking tadalafil 10 mg or 20 mg, respectively, versus 25% in the placebo arm felt treatment improved their erections (p < 0.001), while clinically meaningful increases in IIEF scores (>5) were observed in 56%, 44%, and 13% of groups using tadalafil 20 mg, tadalafil 10 mg, or placebo, respectively (p < 0.001).44 Tadalafil was well tolerated, with 88% of men completing the trial.

Fonseca et al. have reported pooled data from 12 placebo-controlled trials, identifying 637 evaluable men with diabetes.45 Baseline parameters included mean patient age of 57 years and IIEF score of 12.6; compared with 1681 men without diabetes, tadalafil 20 mg improved all primary efficacy outcomes versus placebo, including an average improvement of 7.4 points for the IIEF score and a 53% rate of successful intercourse attempts versus placebo results of 0.9 and 22%, respectively (p < 0.001).45 Treatment effects were independent of type of diabetes, levels and methods of glycemic control, and presence or absence of microvascular complications.

**Efficacy following treatment for prostate cancer**

Clinically meaningful improvements across all primary and secondary end-points (IIEF, SEP questions 2 and 3, EDITS, and GAQ) for on-demand tadalafil 20 mg compared with placebo (p < 0.001) for patients who had a bilateral nerve-sparing radical retropubic prostatectomy were demonstrated in a 33-site, randomized, double-blind, placebo-controlled trial of 303 men with normal preoperative erectile function.46 Successful penetration (SEP question 2) and intercourse attempts (SEP question 3) were reported by 54% and 41% of patients who received tadalafil or a placebo, respectively, while subgroup analysis of 201 men reporting varying degrees of spontaneous postoperative tumescence during baseline intercourse attempts yielded values of 69% and 52% for the same metrics, respectively.46 Tadalafil-treated patients described increased treatment satisfaction as measured by the EDITS questionnaire, and 94.5% completed the study.44 Common side-effects included headache in 21%, dyspepsia in 13%, and myalgia in 7%. Tadalafil has also been shown to be an effective treatment for ED after external beam radiotherapy or brachytherapy for prostate cancer.47,48

Despite advances in the understanding of the underlying mechanisms responsible for post-prostatectomy ED and the well-described rationale for post-prostatectomy penile rehabilitation, there is no consensus regarding the role of PDE-5 inhibitors (alone or in combination with intracavernous injection) for this purpose.49,50 Although several animal studies support the use of PDE-5 inhibitors for the preservation of erectile function and the prevention of corporal fibrosis, veno-occlusive disease, apoptosis, and smooth muscle loss, currently available clinical data are less clear.51–53 Non-randomized, non-controlled studies for on-demand tadalafil, vardenafil,
and sildenafil have demonstrated an improvement for post-prostatectomy potency rates. There is no direct evidence that these compounds improve tissue oxygenation within the corpora; however, these drugs appear to improve the preservation of smooth muscle integrity following cavernosal nerve damage.44

Despite the lack of standardized penile rehabilitation programs, and the need for prospective, placebo-controlled randomized trials and further basic science studies, PDE-5 inhibitors should probably be offered (alone or as part of combination therapy with intracavernous injections) to the informed patient shortly after radical prostatectomy because of potential benefits, ease of use, and patient tolerability.45,56

Tadalafil and antidepressants

A number of studies have demonstrated the association of depression with ED, including the MMAS, which identified this condition as the second most common risk factor for ED; the prevalence of antidepressant-associated ED remains underestimated by physicians, since commonly prescribed agents such as selective serotonin reuptake inhibitors (SSRIs) contribute to sexual dysfunction.46,57,58 Recent evidence-based reviews of contemporary management strategies for these groups indicated that PDE-5 inhibitors appear to be an effective treatment option for depression- and antidepressant-associated sexual dysfunction.49,60 A retrospective, pooled analysis of 19 double-blind, placebo-controlled trials identified 205 men with ED (mean age, 55) receiving antidepressants and tadalafil 10 mg (n = 38), tadalafil 20 mg (n = 113), or placebo (n = 54).44 Common agents included amitriptyline, SSRIs, and venlafaxine. Compared with placebo, improvements were noted in the quality of erections (76 vs 33%), successful intercourse attempts (54 and 59% for tadalafil 10 mg and 20 mg, respectively, vs 25% for placebo) and return to a normal erectile function as defined by an IIEF erectile function score of 26 or more (51.4 and 49.1% vs 11.8%, all p values <0.001).44 Further prospective studies of tadalafil in this cohort are warranted following these initial, encouraging results since diagnosis and treatment of ED improves quality of life in this group and may influence treatment compliance or depressive relapses.

Period of effectiveness

The period of efficacy is the most significant distinguishing clinical characteristic of tadalafil in comparison with sildenafil and vardenafil.41 The extended half-life of tadalafil allows for an expanded window of therapeutic responsiveness, offering the patient more flexibility in the timing of sexual intercourse.41 The time during which a PDE-5 inhibitor is effective is important for patients, since some prefer to engage in sexual activity shortly after taking ED medications, while others prefer to dissociate sexual activity from dosing.41

Tadalafil was examined in two at-home, randomized, placebo-controlled, parallel studies in 348 men with varying etiologies and severity of ED to determine the period of efficacy.42,43 The proportion of successful intercourse attempts (positive response to SEP question 3) at 24 and 36 hours was significantly greater following tadalafil dosing (57 and 60%, respectively) than placebo (31 and 30%, respectively). Patient satisfaction and secondary outcomes for these trials are consistent with the analysis of integrated data, as are studies for duration of clinical effectiveness performed in specific populations such as men with spinal cord injuries.30,63 Product labeling reflects this characteristic, indicating that tadalafil may improve erectile function up to 36 hours following ingestion.25

Daily administration of tadalafil for erectile function

A wealth of clinical experience supports on-demand PDE-5 inhibitors as safe and efficacious agents of choice for first-line treatment of ED in most men; efficacy rates are usually reported in the 60–75% range; however, therapeutic success is often lower in subpopulations identified as more difficult to treat, including diabetics and men with ED following radical prostatectomy.64-67 Patient and partner satisfaction may also be limited by real or perceived lack of treatment flexibility or spontaneity, adverse effects, or improper administration or use of these drugs.67,68 Criteria for therapeutic success, including cure of ED, pleasure, partner satisfaction, reliability, and naturalness, may not be adequately fulfilled by on-demand administration, especially for PDE-5 inhibitors with a shorter therapeutic window of opportunity.68,69 The concept of daily dosing or chronic administration was introduced as treatment alternative for non-responders to on-demand PDE-5 inhibitor therapy and to more closely approximate ‘normal’ erectile function; formalized study of once-daily and chronic dosing schedules suggests that this approach is preferred by a significant proportion of patients, in addition to being an effective salvage strategy for previous non-responders.68,70-78

Mirone et al. reported the first comparative trial of alternative dosing schedules for tadalafil, investigating treatment efficacy and patient preference for tadalafil 20 mg taken on-demand versus three times per week in the dosing European Schedule Use versus on-demand Regimen Evaluation (SURE) study.73 Scheduled dosing was preferred by 42.2% of 3861 men. McMahon reported upon the efficacy, safety, and tolerability of on-demand tadalafil 20 mg versus daily dosed tadalafil 10 mg in 145 men; patients receiving on-demand and daily tadalafil experienced mean improvements of 8.3 and 11.9 for the IIEF, respectively (p<0.001), with changes in the daily-dose group being significantly higher than those in the on-demand group (p<0.05).44 Positive to SEP question 3 responses were noted by 69% and 84% of men in the on-demand and daily tadalafil cohorts, respectively, compared with 50% at baseline (p<0.001), and successful completion of sexual intercourse was statistically higher for daily tadalafil than for the on-demand regimen (p<0.05). Both treatments were well tolerated, with headache, facial flushing, and dyspepsia being the most frequently observed adverse effects.46,71 McMahon also has reported results for efficacy and safety of daily tadalafil in 112 men with ED previously unresponsive to on-demand tadalafil; moderate-to-severe ED was treated with daily
tadalafil at doses of 10 mg and 20 mg for 12 weeks. Tadalafil 10 mg taken daily resulted in a mean improvement of 12.8 and 8.2 from respective baseline and on-demand IIEF scores (p < 0.001), and 58% of intercourse attempts (SEP question 3) were successfully completed (p < 0.001). Improved erections were noted by 69% and 42% of men in the daily and on-demand groups, respectively. Almost half of this study population had diabetes mellitus or concurrent vascular risk factors. Daily tadalafil use resulted in improvements for all efficacy variables and demonstrated a safety profile similar to on-demand treatment, except for the incidence of headache, which was reported more commonly with on-demand use (p < 0.05).

Porst et al. reported a randomized, double-blind, placebo-controlled, parallel-group, 12-week daily-dose study of 268 men, with men assigned 1:2:2 to placebo, tadalafil 5 mg, and tadalafil 10 mg taken once daily. The three groups reported, respectively, changes of 0.9, 9.7, and 9.4 for the IIEF score, successful penetration for 11.2%, 36.5%, and 39.4% of intercourse attempts, completion rates of 13.2%, 45.5%, and 50.1%, and reported rates of improved erections of 28.3%, 84.5%, and 84.6% for placebo, tadalafil 5 mg, and tadalafil 10 mg. Normalization of erectile function (defined as IIEF scores of 26–30) occurred in 8.3, 51.5, and 50.5% of men (all comparisons significant, p < 0.001). Only 8 treated patients discontinued use because of adverse events, of which dyspepsia, headache, back pain, upper abdominal pain, and myalgia were the most common. Buvat et al. recently presented data from a 12-week, randomized, double-blind, placebo-controlled study of 268 men from the UK, Argentina, Brazil, France, and Germany, similarly assigned 1:2:2 to once-a-day placebo, tadalafil 5 mg, or tadalafil 10 mg. Once-daily tadalafil treatment resulted in increased rates of successful intercourse, as well as in significantly more patient satisfaction with erectile rigidity (SEP question 4) and the overall sexual experience (SEP question 5) compared with men reporting successful intercourse and treated with placebo.

Continuous dosing of tadalafil has been shown to improve significantly all commonly utilized treatment outcome measures. To date, the understanding of systemic effects secondary to prolonged continuous administration for the three PDE-5 inhibitors is limited primarily to clinical trials of sildenafil for idiopathic pulmonary hypertension, chronic therapy probably modulates endothelial function, local penile age or pathology-induced changes, and cardiovascular disease, resulting in improved erectile function as a result of effects at both local and systemic levels. In June 2007, the European Commission granted marketing authorization for tadalafil 2.5 mg and 5 mg dosed once daily to treat ED; a starting dose of 5 mg is appropriate for most men.

Patient and partner satisfaction and effect on drug preference

Ultimately, patient preference determines the ED agent of choice. Efficacy, safety, ease of use, cost, and as-yet unidentified factors affect treatment response and treatment satisfaction, with the final decision based on which of the three agents best fulfills the patient’s goals. Although it is tempting to compare efficacy and preference data from different drug trials, this approach is potentially fraught with error owing to differences in research design, clinical end-points, populations, and PDE-5 dosing, delivery, and side-effect profiles. Meaningful comparative data between tadalafil, vardenafil, and sildenafil can only come from properly designed head-to-head trials; however, there are no trials without methodological concerns available at this time.

To date, several comparative studies have been performed in an attempt to gain insight into which erectogenic agent is preferred; although tadalafil fared favorably and was the preferred agent in some of these trials, methodological concerns limit the applicability of these results to the general ED population. The Treatment of ED (TED) trial examined patient and partner preference and satisfaction, as well as physician-rated patient preference, in a real-world, non-interventional multicenter study of 2425 patients who planned to change treatment from tadalafil or sildenafil to the other drug. Despite similar perceptions of treatment effect, preference was primarily based on duration of action and better erections for men choosing tadalafil (1722 out of 2425, 71%) and on better erections and drug tolerance for those choosing sildenafil (Figures 31.5, 31.6). Patients (and partners) who changed from sildenafil to tadalafil or vice versa had greater treatment satisfaction as measured by the Erectile Dysfunction Inventory of Treatment Satisfaction (EDITTS). Further randomized, multicenter comparative studies and the development of a new preference-based disease-specific health-related quality of life instrument for erectile function may better determine ED patients’ drug of choice.

Safety profile

Safety and adverse event profiles for the three clinically approved PDE-5 inhibitors, including tadalafil, are reviewed in detail in Chapter 34, as are the Princeton Consensus Guidelines for sexual dysfunctions and cardiac risk (Chapter 33). It should be emphasized that cardiac safety for PDE-5 inhibitors has been clearly established. While all three agents are contraindicated in men using or requiring nitrates for cardiovascular disease, the concern about on-demand or daily PDE-5 inhibitor use often raises concern about ‘co-administration effects’ in cases of cardiac emergency. Based on clinical experience among thousands of men with ED and cardiovascular risk factors, a cardiac event should be managed at all times in an appropriate environment with little concern related to long- or short-acting agents. All men considering tadalafil therapy should be aware of common side effects, including flushing, headache, congestion, dyspepsia, and myalgia (back ache) (Table 31.2). Although a direct relationship between PDE-5 inhibitors and non-arteric ischemic optic neuropathy has not been establish, up-to-date information should be reviewed, as should recommendations if an adverse event does occur. Finally, no evidence for tachyphylaxis has been demonstrated for PDE-5 inhibitors, including tadalafil.
Figure 31.5  Primary reasons for physician-rated patient treatment preferences. Adapted from BJU Int 2006; 98: 623–9.86

Figure 31.6  Partner-rated treatment preference. Adapted from BJU Int 2006; 98: 623–9.86
Table 31.2 Summary demographics, baseline characteristics, and most common treatment-emergent adverse events

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>Tadalafil 10mg</th>
<th>Tadalafil 20mg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>638</td>
<td>321</td>
<td>1143</td>
<td>2102</td>
</tr>
<tr>
<td><strong>Mean (range) or n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>57 (22–81)</td>
<td>58 (26–81)</td>
<td>56 (22–88)</td>
<td>56 (22–88)</td>
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<tr>
<td>Age &gt;65 years</td>
<td>140 (22)</td>
<td>96 (30)</td>
<td>248 (22)</td>
<td>484 (23)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27.3 (18.1–53.7)</td>
<td>27.9 (18.2–46)</td>
<td>27.3 (12.7–52)</td>
<td>27.4 (12.7–53.7)</td>
</tr>
<tr>
<td>Duration of ED of ≥12 months</td>
<td>572 (90)</td>
<td>280 (87)</td>
<td>1006 (88)</td>
<td>1858 (88)</td>
</tr>
<tr>
<td><strong>Cause of ED, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organic</td>
<td>369 (58)</td>
<td>215 (67)</td>
<td>627 (55)</td>
<td>1211 (58)</td>
</tr>
<tr>
<td>Psychogenic</td>
<td>82 (13)</td>
<td>20 (6)</td>
<td>147 (13)</td>
<td>249 (12)</td>
</tr>
<tr>
<td>Mixed</td>
<td>187 (29)</td>
<td>86 (27)</td>
<td>369 (32)</td>
<td>642 (31)</td>
</tr>
<tr>
<td><strong>IIEF EF severity, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (26–30)</td>
<td>33 (5)</td>
<td>16 (5)</td>
<td>39 (3)</td>
<td>88 (4)</td>
</tr>
<tr>
<td>Mild (17–25)</td>
<td>212 (33)</td>
<td>113 (35)</td>
<td>425 (37)</td>
<td>750 (36)</td>
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<tr>
<td>Moderate (11–16)</td>
<td>171 (27)</td>
<td>84 (26)</td>
<td>303 (27)</td>
<td>558 (27)</td>
</tr>
<tr>
<td>Severe (1–10)</td>
<td>220 (34)</td>
<td>107 (33)</td>
<td>376 (33)</td>
<td>703 (33)</td>
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<tr>
<td><strong>Medical history, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>33 (5)</td>
<td>17 (5)</td>
<td>62 (5)</td>
<td>112 (5)</td>
</tr>
<tr>
<td>Depression</td>
<td>23 (4)</td>
<td>15 (5)</td>
<td>53 (5)</td>
<td>91 (4)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>130 (20)</td>
<td>68 (21)</td>
<td>223 (20)</td>
<td>421 (20)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>110 (17)</td>
<td>51 (16)</td>
<td>166 (15)</td>
<td>327 (16)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>189 (30)</td>
<td>90 (28)</td>
<td>337 (29)</td>
<td>616 (29)</td>
</tr>
<tr>
<td><strong>Reason for discontinuance, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completed</td>
<td>554 (86.8)</td>
<td>284 (88.5)</td>
<td>1025 (89.7)</td>
<td></td>
</tr>
<tr>
<td>Adverse event</td>
<td>8 (1.3)</td>
<td>5 (1.6)</td>
<td>36 (3.2)</td>
<td></td>
</tr>
<tr>
<td>Lack of efficacy</td>
<td>32 (5)</td>
<td>4 (1.3)</td>
<td>18 (1.6)</td>
<td></td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>16 (2.5)</td>
<td>4 (1.3)</td>
<td>14 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Patient decision</td>
<td>16 (2.5)</td>
<td>12 (3.7)</td>
<td>26 (2.3)</td>
<td></td>
</tr>
<tr>
<td>Protocol violation</td>
<td>9 (1.4)</td>
<td>4 (1.3)</td>
<td>10 (1)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>3 (0.5)</td>
<td>8 (2.8)</td>
<td>10 (1)</td>
<td></td>
</tr>
<tr>
<td><strong>Overall safety, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects within one or more treatment-emergent adverse event</td>
<td>247 (39)</td>
<td>185 (58)</td>
<td>577 (51)</td>
<td></td>
</tr>
<tr>
<td>Discontinuation for adverse event</td>
<td>8 (1.3)</td>
<td>5 (1.6)</td>
<td>36 (3.2)</td>
<td></td>
</tr>
<tr>
<td><strong>Most common treatment-emergent adverse events, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>30 (5)</td>
<td>38 (12)</td>
<td>175 (15)</td>
<td></td>
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<tr>
<td>Dyspepsia</td>
<td>7 (1)</td>
<td>23 (7)</td>
<td>9 (8)</td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>15 (2)</td>
<td>20 (6)</td>
<td>60 (5)</td>
<td></td>
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<tr>
<td>Nasopharyngitis</td>
<td>24 (4)</td>
<td>26 (8)</td>
<td>23 (2)</td>
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<tr>
<td>Myalgia</td>
<td>6 (1)</td>
<td>16 (5)</td>
<td>33 (3)</td>
<td></td>
</tr>
<tr>
<td>Flushing</td>
<td>8 (1)</td>
<td>10 (3)</td>
<td>39 (3)</td>
<td></td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>4 (1)</td>
<td>11 (3)</td>
<td>28 (2)</td>
<td></td>
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<tr>
<td>Pain in limb</td>
<td>5 (1)</td>
<td>10 (3)</td>
<td>31 (3)</td>
<td></td>
</tr>
</tbody>
</table>

Patients were included based on a history of erectile dysfunction (ED). Subsequent assessment of ED by the International Index of Erectile Function (IIEF) at baseline showed that a small proportion of men (4%) had an IIEF domain score of ≥26 (ED). The cause of ED was determined by the investigators based on patient history, physical examination findings and any previous diagnostic testing. Adverse events were coded using the MedRA dictionary (version 5.0). EF: Erectile function; with permission from reference 87, adapted from BJU Int.
Conclusion

Tadalafil significantly improves erectile function in men with ED of varying severity and etiology when taken on-demand prior to sexual activity, 5 mg daily, or on a chronic (20 mg three times per week) basis. Clinical trials have demonstrated that tadalafil is well tolerated, safe and an important therapeutic option for physicians treating men with ED. Administration is simplified by an extended period of effectiveness and the absence of interaction with food or alcohol consumption, offering added clinical benefit to patients by allowing freedom to choose when intercourse will take place and reducing performance anxiety associated with time constraints. Patients and partners report satisfaction with penile rigidity, time to onset, and reliability of treatment effect. Given the emerging data for improvement in endothelial function, general vascular health, and its potential to salvage erectile function in men demonstrating an unsatisfactory initial response to on-demand PDE-5 inhibitors, once-daily dosing offers an important primary and salvage treatment strategy.

REFERENCES

82. La Vignera S, Calogero AE, Cannizzaro MA, et al. Tadalafil and modifications in peak systolic velocity (Doppler spectrum dynamic analysis) in the cavernous arteries of patients with type 2 diabetes
90. Tolra JR, Campana JM, Ciutat LF, Miranda EF. Prospective, randomized, open-label, fixed-dose, crossover study to establish preference of patients with erectile dysfunction after taking the three PDE-5 inhibitors. J Sex Med 2006; 3: 901–9.
Vardenafil: a biochemically potent phosphodiesterase type 5 inhibitor

Sharron H Francis and Jackie D Corbin

Introduction

In 2003, vardenafil hydrochloride was introduced to the world market as a new oral therapy for treatment of erectile dysfunction (ED). It was marketed as vardenafil hydrochloride trihydrate under the brand name Levitra® by Bayer Pharmaceuticals Corporation and is presently used under licence by GlaxoSmithKline and Schering Corporation. It rapidly gained approval in countries around the world as a safe and effective treatment for ED. The chemical name for vardenafil is piperazine, 1-[[3-(1,4-dihydro-5-methyl-4-oxo-7-propylimidazo[5,1-f][1,2,4]triazin-2-yl)-4-ethoxyphenyl] sulfonyl]-4-ethyl-, monohydrochloride trihydrate (Figure 32.1), the empirical formula is C_{26}H_{30}N_3O_S.HCl.3H_2O, and the molecular weight is 579.1g/mol. Vardenafil, the active agent, is a potent inhibitor of phosphodiesterase (PDE) type 5, which breaks down cGMP in cells.

cGMP and vardenafil in penile erection

Penile erection is mediated by elevation of cGMP in smooth muscle cells of the penile vasculature in response to erogenous stimuli that induce the release of nitric oxide (NO) from nitrergic neurons or endothelial cells that line the blood vessels (Figure 32.2).2,3 Cyclic GMP interacts with cGMP-dependent protein kinase (PKG), which phosphorylates a number of proteins leading to lowering of intracellular calcium through increased calcium extrusion from the cell and increased sequestration of calcium in intracellular stores, as well as desensitizing cells to calcium; this effect decreases contractile tone in the smooth muscle and promotes vasodilatation (see Figure 32.2).4 The level of cGMP in cells such as the smooth muscle cells of the corpus cavernosum and penile arteries is determined by a balance between its synthesis from GTP (by enzymes known as guanylyl cyclases) and its breakdown (by cGMP PDEs such as PDE-5).5 The action of PDE-5, which is highly abundant in penile vascular tissues, blunts or blocks cGMP elevation and the erectile response to erogenous stimuli (see Figure 32.2).6 The appropriate balance between cGMP synthesis and breakdown is critical for normal erectile function; many patients suffering from ED have a biochemical imbalance in this process, either too little synthesis of cGMP or excessive hydrolysis of cGMP, which can lead to ED. The therapeutic effect of vardenafil is due to its inhibition of PDE-5 hydrolysis of cGMP, thereby fostering improved penile tumescence.5

Vardenafil inhibition of PDE-5

Vardenafil mimics the PDE-5 substrate, cGMP, and spatial components of the vardenafil molecule compete directly with cGMP for access to the catalytic pocket of this enzyme (Figure 32.3). The overall structure of vardenafil bears some resemblance to that of cGMP, as can be seen in Figures 32.3a and 32.3b; Figure 32.3b displays space-filling models to depict more accurately the molecular features of cGMP and vardenafil; in cGMP, the guanine and the cyclic phosphate ring that is appended to the ribose provide critical determinants for interaction with the PDE-5 catalytic site. The ribose does not make particularly important contacts with the enzyme. Cyclic GMP is shown in the anti conformation, which evidence suggests is the orientation of the ribose and phosphate moieties when the substrate is bound to the PDE-5 catalytic site. Vardenafil lacks the cyclic phosphate ring that is acted on by the catalytic machinery of the enzyme, but the bicyclic ring in vardenafil mimics the guanine in cGMP (see Figure 32.3), and evidence suggests that it exploits many of the contacts that the guanine makes with the PDE-5 catalytic site. The orientation of the piperazine ring in vardenafil shown here is based on that reported earlier for sildenafil. The potency (affinity) of vardenafil to inhibit PDE-5 catalytic activity (half maximum inhibitory concentration, IC_{50} = 0.09nM) was determined to be about 25,000-fold greater than the affinity of the enzyme for cGMP (K_m = 2.5µM),7 and this high affinity of vardenafil for the PDE-5 catalytic site was independently verified in direct binding studies using [3H]vardenafil in the absence of the competing cGMP substrate.7 The exceptionally high affinity interaction between PDE-5 and vardenafil is provided by multiple structural features of vardenafil that are absent in cGMP and that exploit additional contacts with amino acid side chains in the PDE-5 catalytic site,6,9 by contacts that are formed with amino acids located in close proximity to the catalytic site, and by influences external to the catalytic site (see below).10 Vardenafil is highly selective for inhibition of PDE-5 compared with other PDEs; it has a more than 15-fold lower potency for inhibition of the photo-receptor PDE-6 family, more than 130-fold lower potency for inhibition of the PDE-1 family, more than 300-fold lower
potency for inhibition of the PDE-11 family, and more than 1000-fold lower potency for inhibition of the PDE-2, PDE-3, PDE-4, PDE-7, PDE-8, PDE-9, and PDE-10 families. Owing to the effects of differences in the distribution of nitrogen and carbon atoms in the bicyclic ring of vardenafil compared with the guanine of cGMP, some contacts may be stronger and, along with some ‘extra’ contacts, may contribute to the higher affinity of PDE-5 for vardenafil over cGMP (see below).

cGMP and vardenafil following interaction with PDE-5 catalytic site

The fates of cGMP and vardenafil differ when each enters the PDE-5 catalytic site. When cGMP enters the catalytic site, the cyclic phosphate ring is quickly hydrolyzed by the PDE-5 catalytic machinery to produce 5′-GMP (Figure 32.4). 5′-GMP has very low affinity for the PDE-5 catalytic site (about 1-5mM) and rapidly dissociates from the catalytic pocket. In contrast, when vardenafil binds to the PDE-5 catalytic site, it is not modified; therefore, its potency is preserved and dissociation is very slow. Furthermore, following dissociation, it has the potential to rebind immediately to the PDE-5 catalytic site (as shown by the double-ended arrow in Figure 32.4) since it is structurally intact. This characteristic is true of all the PDE-5 inhibitors currently in clinical use for treatment of ED. Therefore, the effect of vardenafil (as well as that of sildenafil and tadalafil) to block cGMP access is amplified by the fact that these features contribute to a longer occupancy of the catalytic site by the inhibitors. Vardenafil does not interact with the allosteric cGMP-binding site in the regulatory domain of PDE-5 (see Figure 32.4) because this site is structurally very different from the PDE-5 catalytic site and is highly rigorous in its specificity for cGMP and closely related nucleotides. The topography of the allosteric cGMP-binding site excludes vardenafil access.

Potency of vardenafil

Vardenafil is 10- to 40-fold more potent than either sildenafil, which was already in clinical use for treatment of ED when vardenafil was licenced for use (Figure 32.5), or tadalafil, which was introduced later. The higher potency of vardenafil for PDE-5 inhibition accounted, at least in part, for its lower range of dosing options (2.5 mg, 5 mg, 10 mg, and 20 mg) compared with that for sildenafil (25 mg, 50 mg, and 100 mg).
or tadalafil (5 mg, 10 mg, and 20 mg). The higher potency of vardenafil may also account for its effectiveness in treating patients with severe ED and those who had unsatisfactory results with sildenafil. For most patients, the recommended starting dose of vardenafil is 10 mg to be taken about 1 hour prior to sexual activity, although certain medical conditions may warrant a lower beginning dose (see below).  

As with all PDE-5-selective inhibitors, sexual arousal is required to increase cellular synthesis of cGMP and to allow for the action of vardenafil to enhance cGMP accumulation by blocking its breakdown and thereby improve penile tumescence (see Figure 32.2). Despite the significantly higher inhibitory potency (IC\textsubscript{50}) of vardenafil for PDE-5 than that for sildenafil or tadalafil (IC\textsubscript{50} values of 0.09 nM, 3.7 nM, and 1.8 nM, respectively), the clinical efficacy, ease of use, and patient satisfaction for the three medications appears to be similar. This would not be intuitively predicted, but the comparable efficacy despite a lower dosing regimen (see above) may have explanations in the basic functional properties of PDE-5 and the higher affinity of the enzyme for vardenafil. The inhibitor concentration in the cytosol is expected to equal that in the plasma (peak plasma concentration following vardenafil 20 mg was determined to be about 30 nM of which about 1.5 nM is estimated to be free). As soon as any of the three inhibitors enters the cell, it is predicted to be bound immediately by PDE-5. The high affinity of interaction between PDE-5 and each of the inhibitors would tend to sequester the inhibitor and maintain low cytosolic concentration; this effect would assist in maintaining a high gradient between the plasma and cytosol, thereby favoring continued entry of the inhibitor until PDE-5 is saturated. As a result, the action of PDE-5 inhibitors that exhibit such high potency may be less influenced by plasma concentration than is thought.

**Pharmacokinetics**

Vardenafil has proven to be an effective, safe, and reliable oral treatment for ED in a broad spectrum of patients. In 2003, a report from a multicenter, randomized, double-blind, placebo-controlled study employing three vardenafil dosages (5 mg, 10 mg, and 20 mg) in 580 patients (aged from 45 to
Vardenafil: a biochemically potent phosphodiesterase type 5 inhibitor

![Diagram of PDE-5 structure](image)

**Figure 32.4** Working model of the structure of phosphodiesterase (PDE) type 5. PDE-5 comprises two identical kDa monomers, each of about 98 kDa. Each monomer contains a more carboxyl-terminal catalytic domain where breakdown of cGMP (shown as a black ball) occurs and the product, 5’-GMP (shown as a black half-moon) is released. Each subunit also contains a more amino-terminal regulatory domain that contains allosteric cGMP-binding sites that are biochemically and evolutionarily distinct from the catalytic site. Vardenafil binds only to the catalytic site and inhibits catalysis by competing with cGMP for access to the catalytic pocket. Unlike cGMP, vardenafil is not modified by the PDE-5 catalytic site.

over 65 years) with ED of varying severity resulting from organic, psychogenic, or mixed etiologies indicated that vardenafil treatment (all doses) improves reliability of achieving an erection sufficient for penetration, orgasmic function, and persistence of the erection for a period long enough for satisfactory intercourse.19 Other placebo-controlled studies testing the effectiveness of vardenafil in treatment of ED in large groups of diverse patients reached similar conclusions.20-23 A recent study reported that vardenafil treatment for 12 of 26 weeks restores normal erectile function in a substantial percent of men with general ED irrespective of the severity, etiology, age, or duration of ED.18

Vardenafil is rapidly absorbed, has a bioavailability of about 15%, and is extensively metabolized on the first pass through the liver (Table 32.1). Vardenafil and its main metabolite (N-desethyl vardenafil) are distributed throughout most body tissues and are highly (about 95%) adsorbed, albeit reversibly, to plasma proteins. Since vardenafil is distributed extensively in body tissues, it is expected that any tissue containing PDE-5 has the potential to be affected by vardenafil as well as by other PDE-5 inhibitors such as sildenafil, tadalafil, and udenafil. In the fasting state, onset of action following ingestion of vardenafil is about 0.5–2 hours, with a median of 1 hour, which is similar to the profile for sildenafil and tadalafil.24-28 In a placebo-controlled study of 372 men, an erection sufficient for successful intercourse was reported to occur in some patients as early as 10 minutes after dosing with either 10mg or 20mg, and about 50% of patients have a successful result within 25 minutes after dosing.24 However, given the variation in the time of onset (10–60 minutes), first-time users are advised to take vardenafil an hour prior to initiating sexual activity.26 Onset of action correlates well with the peak concentration, which occurs within 0.5–2 hours of administration in the fasted state (see Table 32.1).25 Consumption of a high-fat meal preceding ingestion of the medication was shown to delay absorption substantially, by up to 1 hour, and also to reduce the peak concentration, but a moderate-fat meal has little or no effect and is not considered to be a clinical concern.29

The duration of the effect of vardenafil has not been extensively studied. Typically, the pharmacological effectiveness of a medication wanes quickly as the medication is cleared from the plasma.30 However, many drugs either act at cell surfaces or act with relatively low affinities on target proteins inside cells. Vardenafil not only acts inside cells, it does so by binding with very high affinity to PDE-5. Vardenafil is not believed to
Figure 32.5 Comparison of the molecular structures of vardenafil and sildenafil. The two positions that differ in vardenafil and sildenafil are indicated by the dotted circles. The pKₐ values shown here were experimentally determined.¹⁸ IC₅₀, half maximum inhibitory concentration; pKₐ, the acid dissociation constant.

### Table 32.1 Pharmacokinetics of vardenafil

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Vardenafil 10mg</th>
<th>Vardenafil 20mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area under the curve (µg/hour/l)</td>
<td>32.6±1.59</td>
<td>74.5±1.82</td>
</tr>
<tr>
<td>Cmax (µg/l)</td>
<td>9.05±1.63</td>
<td>20.9±1.83</td>
</tr>
<tr>
<td>Half-life (hours)</td>
<td>4.18±1.27</td>
<td>3.9±1.31</td>
</tr>
<tr>
<td>Tmax (hr)</td>
<td>0.92 (0.25–2.5)</td>
<td>0.66 (0.25–3.0)</td>
</tr>
<tr>
<td>Absolute bioavailability (%)</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Protein binding (%)</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>Mean steady-state volume of distribution (l)</td>
<td>208</td>
<td></td>
</tr>
<tr>
<td>Effect of high-fat meals on Cmax (%)</td>
<td>18–50%</td>
<td></td>
</tr>
<tr>
<td>Site of metabolism</td>
<td>Hepatic</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Contribution of metabolite to effect (%)</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Excretion (% of dose)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feces</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>Urine</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

Cmax; maximum concentration; Tmax, time to Cmax. Values compiled from reference 26.

be degraded within smooth muscle cells. Therefore, this unusual mechanism could lead to trapping of vardenafil inside smooth muscle cells in the penis, which could extend its duration of action well beyond that predicted from its half-life in the plasma. Thus, for intracellular-acting, high-affinity drugs such as vardenafil, the duration of action should depend on intracellular half-life, not plasma half-life. Although it would be predicted that intracellular half-life of different drugs would be proportional to their affinities for the receptor, other factors could mitigate this prediction.

The half-life of vardenafil in the plasma following oral administration was determined to be about 4 hours in fasted patients suffering from ED (see Table 32.1);³⁵ however, in a randomized, double-blind, placebo-controlled, flexible-dose study of 383 men with ED treated with different dosages of vardenafil (5 mg, 10 mg, or 20 mg) and asked to initiate sexual activity 8 hours later, a significant number of patients reported that the effect of vardenafil to improve erections was still functional at a time (8–10 hours after dosing) when plasma vardenafil levels should have been less than 25% of the peak concentration, which is usually associated with optimal pharmacological action.³⁵ More rigorous analysis of this phenomenon is required to understand more fully the pharmacodynamics involved not only with vardenafil, but also with the other PDE-5 inhibitors used for the treatment of ED, since sildenafil and tadalafl also show persistence of action beyond the time that would be predicted based on plasma clearance time.³²,³³

Vardenafil is metabolized primarily in the liver by cytochrome P4503A4 (CYP3A4) and to some extent by CYP3A5 and CYP2C9. The major circulating metabolite is produced by removal of the ethyl group from the vardenafil piperazine ring. In plasma, the main metabolite is also found largely as the glucuronidated form but the non-glucuronidated metabolite represents about 26% of the parent compound. The main metabolite of vardenafil contributes to the bioactivity (about 7% of the pharmacological effect), is subject to further metabolism, and exhibits a similar selectivity profile among mammalian PDEs, albeit with a roughly 28% lower potency for PDE-5 than vardenafil.¹¹

Plasma clearance of both the parent compound and the major metabolite occurs with a half-life of about 4 hours; the major metabolites are primarily removed by extrusion into the biliary duct and excretion in the feces, with a small amount eliminated in the urine. Clearance is significantly slowed in patients suffering from hepatic insufficiency or when vardenafil is taken along with other medications that are competitively metabolized by the cytochromes; these include ritonavir, indinavir, ketoconazole, itraconazole, and erythromycin.¹¹ In these situations, recommended dosage is reduced significantly and frequency of administration must be lessened. Co-administration of ritonavir and vardenafil was shown to cause a 13-fold increase in peak concentration of vardenafil and prolonged the half-life of vardenafil in plasma to 26 hours. Other factors such as aging also slow clearance and therefore warrant adjustment in the dosage protocol.
Side-effects

Use of vardenafil for treatment of ED is well tolerated by most patients.1,4,14-20,22,24 Vardenafil is highly selective for PDE-5 except for slight cross-reaction with PDE-6 (see below), and it has not been shown to interact with other cellular proteins. This high specificity and affinity of vardenafil for PDE-5 is consistent with the limited number of side-effects that have been reported and with the low concentration of the inhibitor required for improvement of erectile function. The most common side-effects, which are experienced by a small percentage (<15%) of patients, include headache, facial flushing, stuffy nose, dyspepsia, sinusitis, dizziness, and nausea; all of these are typically mild to moderate in severity, transient, and infrequent as the basis for discontinuation of use of the medication. Most of these effects are either constant during the course of the use of the medication or decline over time. Most of these common adverse effects are thought to be due to vardenafil inhibition of PDE-5 activity in the smooth muscle of the blood vessels or other smooth muscle, such as that which forms the sphincters and the wall of the gastrointestinal tract.

The effect of vardenafil on systemic cardiovascular function is modest and there have been few if any concerns regarding cardiovascular safety issues. Following administration of vardenafil (20mg), systolic and diastolic blood pressure declines by 7mmHg and 8mmHg, respectively, and is accompanied by a slight increase in heart rate (4 beats per minute). In some people, vardenafil, like sildenafil, causes a dose-related disturbance of blue–green color discrimination; the effect is transient and most obvious within 1 hour of taking the medication.1,11 The visual perturbation is thought to be due to the effect of vardenafil to inhibit the catalytic activity of photoreceptor PDEs, which are members of the PDE-6 family and are highly homologous in amino acid sequence to the PDE-5 family. Non-arteritic anterior ischemic optic neuropathy, which results in loss or decrease in vision, has been reported in a very small number of patients taking PDE-5 inhibitors, including vardenafil. However, the risk factors for ED and non-arteritic ischemic optic neuropathy are very similar, and a causal role of these medications in the few cases of the optic neuropathy is not established.35

Contraindications

In addition to the cautions described above regarding concomitant use with CYP3A4 inhibitors, the use of vardenafil with nitrovasodilators, either regularly or intermittently, is also contraindicated. This includes prescription medications such as nitroglycerin and some recreational drugs (poppers) that contain amyl nitrate and butyl nitrate. As with the NO released from penile neurons or endothelial cells (see Figure 32.2), NO released from nitroglycerin or certain recreational drugs increases guanylyl cyclase activity in vascular smooth muscle and so leads to increased synthesis of cGMP; the action of these agents to increase production of cGMP therefore synergizes with the action of PDE-5 inhibitors such as vardenafil to block cGMP breakdown (see Figure 32.4), and the resulting increase in cellular cGMP can be dramatic and can produce pronounced systemic hypotension and tachycardia, both of which can be life-threatening. Co-administration of vardenafil with various medications prescribed to lower blood pressure elicits only modest lowering of systemic blood pressure; however, caution is advised when vardenafil is co-administered with alpha-blockers, which are commonly prescribed for blood pressure control or treatment of benign prostatic hyperplasia.1 In addition, men who have conditions that predispose them to priapism (e.g. sickle cell anemia) or who have anatomical deformation of the penis should use PDE-5 inhibitors, including vardenafil, with caution.

Mechanism of action

Vardenafil competes with cGMP for access to the catalytic site of PDE-5, thereby blocking breakdown of cGMP (see Figure 32.4).27 It is highly selective for PDE-5 over other PDEs, thereby restricting its action to tissues containing PDE-5 and other proteins that provide for cGMP signaling. The selective and potent interaction of vardenafil with the catalytic site of PDE-5 is most likely due to unique features in both. Vardenafil potency for inhibition of PDE-5 (IC50) is about 25,000-fold higher (IC50 = 0.99nM) than the affinity of the substrate cGMP (Km = 2.5μM).28 The much higher affinity of the PDE-5 catalytic site for vardenafil provides for the very effective pharmacological action of this medication. Vardenafil, like sildenafil and tadalafil, does not interact with the allosteric cGMP-binding site on PDE-5; nor does it interact with allosteric cGMP-binding sites either on the PKG, cGMP-gated cation channels or on other cellular proteins.

This high selectivity for the catalytic site of PDE-5 is due to the fact that this site is evolutionarily and biochemically distinct from cGMP-binding sites in proteins other than members of the PDE superfamily.4 To date, vardenafil has not been shown to potently interact with cellular proteins other than PDE-5. Therefore, the novel topography of the PDE-5 catalytic site and the unique chemical characteristics of the vardenafil molecule provide for highly selective and potent interaction. The very high affinity of PDE-5 for vardenafil is provided by contacts within the catalytic site that are shared by cGMP and other inhibitors. However, novel contacts that are uniquely provided by the structure of vardenafil and its effect on the protein exploit interactions that the other inhibitors and cGMP cannot make (see below).

Structural features that contribute to the higher potency of vardenafil over sildenafil

X-ray crystal structures of isolated PDE-5 catalytic domain in complex with vardenafil or sildenafil reveal a similar mode of binding.8 Initially this result was puzzling since the potencies differ by 10- to 40-fold.7 This conundrum was recently resolved when our group demonstrated that in the isolated catalytic domain of PDE-5, vardenafil and sildenafil have similar potencies so it is not surprising that they share a 'similar mode of binding'.29 The potency of sildenafil for
PDE-5 inhibition is the same for PDE-5 holoenzyme and the isolated catalytic domain; however, the potency of vardenafil is significantly greater for the holoenzyme than for the isolated catalytic domain (Figure 32.6). Thus, it is clear that the higher potency of vardenafil over sildenafil in the PDE-5 holoenzyme is provided by the influence of the regulatory domain on the catalytic site to optimize interaction with the unique chemical properties of vardenafil. The molecular mechanism that provides for this effect is not known, but it is clearly of considerable importance in drug design.

The structural features of sildenafil and vardenafil appear to be quite similar, but the greater potency of vardenafil and the novel requirement for the PDE-5 regulatory domain to exhibit higher potency indicates that there are substantial differences. Sildenafil and vardenafil differ in having:

- an ethyl or methyl group appended to the piperazine side chain;
- a carbon or nitrogen at position 2 in the 5-member ring; and
- a carbon or nitrogen at position 3 in the 5-member ring.

Differences are indicated in Figure 32.5 by the dotted-line circles. Analogs of vardenafil and sildenafil were used to show that the potency difference is not due to the ethyl–methyl group appended to the respective piperazine rings. This indicates that the altered distribution of the carbon and nitrogen atoms in the bicyclic ring systems of these inhibitors in combination with the influence of the PDE-5 regulatory domain provides for the difference in potency; the bicyclic rings are more accurately described as an imidazotriazinone ring in vardenafil and a pyrazolopyrimidinone ring in sildenafil.

The variation in location of the nitrogen and carbon atoms in the respective bicyclic rings has an impact on the pKₐ of titratable groups (see Figure 32.5), the distribution and density of electrons in the rings, and perhaps other features. In general, the influence of a strong dipole moment (or polarization) in purines contributes importantly to stacking interactions with phenylalanine or tryptophan in proteins; the polarization of electrons intrinsic to a particular purine such as cGMP or a purine-like molecule generates a characteristic dipole moment that can differentially induce polarization in the aromatic side chains of certain amino acids. This ‘polarizing power’ is influenced both by exocyclic substituents on a purine-like ring, such as the carbonyl oxygen of cGMP, vardenafil, or sildenafil, and by nitrogens in the bicyclic ring. If the polarizing power of vardenafil is greater than that of sildenafil, this may induce greater polarization in the side chains of amino acids such as Phe-786, Phe-820, and Tyr-612 in the PDE-5 holoenzyme, thereby enhancing hydrophobic interactions between these residues and the vardenafil bicyclic ring.

The importance of each of the three most prominent amino acid contacts (Gln-817, Phe-820, and Tyr-612) was quantified using site-directed mutagenesis of the PDE-5 holoenzyme (Figure 32.7); individual replacement of any of these by alanine causes significantly greater loss in vardenafil potency than in sildenafil potency. Binding contact of inhibitor with Phe-820 or Tyr-612 involves hydrophobic interactions; the side chain of Phe-820 forms stacking interactions with the five-member ring of each of the inhibitors. If the polarizing power of vardenafil substantially exceeds that of sildenafil, the binding pattern in X-ray crystal structures may indeed be similar, but a difference in the strength of those bonds could still exist in the context of the holoenzyme.

Vardenafil or sildenafil also contacts the hydroxyl of Tyr-612 through a water molecule that contacts the nitrogen at position N-3 or N-2 in the respective five-member ring (see Figure 32.7). This water molecule is hydrogen-bonded to the Tyr-612 hydroxyl and another water to form a water-bridge with the zinc in the catalytic site. Differences in the strength of this bond may also have an impact on potency. The electronegativity of the nitrogen atom of the vardenafil 5-member ring (indicated by an arrow in Figure 32.5) was experimentally determined to be about 100-fold greater than that of the nitrogen atom of sildenafil 5-member ring (see Figure 32.5).
nitrogen in the same position of sildenafil.\textsuperscript{37} This clearly indicates different patterns of charge distribution in these drugs that could affect both the effectiveness of each to polarize catalytic site amino acids and to form strong hydrogen bonds with the water-bridge. In addition, the nitrogen adjoining the carbonyl oxygen in the six-member ring of the sildenafil bicyclic ring is about three-fold more electronegative than the homologous nitrogen in vardenafil. These differences refute the concept that the chemical properties of these inhibitors are essentially the same. Nevertheless, in the absence of the PDE-5 regulatory domain, these are not sufficient to provide for different potencies.\textsuperscript{10}

Conclusion

Vardenafil continues to be the most biochemically potent PDE-5-selective inhibitor in clinical use for treatment of ED.

Acknowledgments

Supported by NIH DK40299 and DK58277.

\begin{thebibliography}{99}
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The Princeton Guidelines for treatment

Graham Jackson

Introduction

With the increasing evidence linking erectile dysfunction (ED) to coronary artery disease, a panel of experts was convened in Princeton in 1999 in order to create guidelines for treatment of ED in men with cardiac disease.\(^1\) Criteria for stratifying men into low-risk, indeterminate-risk (also intermediate-risk) and high-risk groups were developed based on the evidence available at that time, and treatment strategies were recommended in a practical clinical context. The guidelines were well received, having a significant impact on the medical profession and lay community and dispelling the fear that wrongly linked sex and the treatment of ED in cardiac patients with potentially fatal consequences.

Over time, several landmark papers established that the link between ED and coronary artery disease is endothelial dysfunction and, importantly, that the ED presentation may occur 2–3 years ahead of a cardiac event.\(^2,3\) ED came to be recognized as a marker for silent coronary artery disease and to be considered a ‘cardiovascular equivalent’.\(^4\) In response, in 2004 the Second Princeton Consensus Conference was convened and the panel revisited the treatment recommendations and algorithms, updating them on the basis of the evidence accrued since 1999.\(^5\) These recommendations have been presented and published but are briefly summarized in this chapter.

Clinical management guidelines

As the knowledge and evidence base associating ED with coronary artery disease became firmly established, the second Princeton (Princeton II) paper focusing on cardiac risk concluded that ‘a man with ED and no cardiac symptoms is a cardiac (or vascular) patient until proved otherwise’.\(^6\) This fundamental concept emphasizes the importance of evaluating the ED patient ‘beyond the penis’ but also challenges cardiologists to consider sexual activity and ED as part of their routine patient evaluation. Just as there is more to sex than an erect penis, there is more to ED evaluation than simply restoring an erection.

The Princeton II Guidelines include an algorithm for evaluating cardiac risk (Figure 33.1). The algorithm maintains the low-, indeterminate-, and high-risk groupings, which are expanded upon in Table 33.1. One of the key points here is not to deny sexual activity or ED therapy based on risk but to evaluate the risk and lower it if possible to facilitate sexual intercourse or ED therapy. Closing the door to sexual activity prematurely does not constitute good medical practice – it is not a crime to be unsure of what to do, so referral is strongly recommended.

The man presenting with erectile dysfunction

Atherosclerosis of the coronary arteries shares the same risk factors as ED. All men presenting with ED and no cardiac history should have a cardiac history taken. Asking about effort-induced chest pain or breathlessness should be complemented with a check of the family history, smoking habits, and any suggestion of hypertension. Is he overweight, what exercise does he take, and is he on any medication? More subtle signs include recent increased fatigue, falling asleep easily watching television, irritability, and being unusually short-tempered. Clinical examination is usually normal but occasionally murmurs are heard, carotid or femoral bruits detected, peripheral edema noted, and the blood pressure found to be raised (over 140/90 mmHg). Routine investigations should include a fasting glucose and lipid profile, and any evidence of the metabolic syndrome should be acted upon with appropriate referrals. In the era of technology, ‘old-fashioned clinical medicine’ remains the basis for directing further tests.

The cardiac patient

ED affects over 50% of cardiac patients but cardiologists and family doctors rarely ask about sex or ED.\(^6,7\) The Algorithm in Figure 33.1 and Table 33.1 offers practical guidelines but clearly is useless if the subject is not raised by the healthcare professional or patient. The importance of lifestyle modification as part of the management was emphasized by the Princeton Panel (see Chapter 15) and by encouraging the patient to contribute to his treatment, it establishes a contract between the healthcare professional and patient that should promote benefit.

Cardiovascular response to sexual activity

Several studies performed using ambulatory electrocardiography (ECG) and blood pressure monitoring have compared
Figure 33.1  The Princeton II algorithm for the evaluation of men with erectile dysfunction (ED).

The heart rate, ECG, and blood pressure responses to sexual activity with the responses to other normal daily activities. The energy requirement during sexual intercourse is not excessive for couples in a longstanding relationship. The average peak heart rate is 110–130 beats per minute and the peak systolic blood pressure is 150–180mmHg. Expressed as a multiple of the metabolic equivalent (MET) of energy expenditure expanded in the resting state (1 MET), sexual intercourse is associated with a work load of 2–3 METs before orgasm and 3–4 METs during orgasm. Younger couples, who are not usually the people we advise, may be more vigorous in their activity, expending 5–6 METs. The average duration of sexual intercourse is 5–15 minutes. Therefore, sexual intercourse is not an extreme or sustained cardiovascular stress for patients in a longstanding relationship who are comfortable with each other. Casual sexual intercourse, which must be separated from extramarital sexual intercourse with a longstanding ‘other partner’, may involve a greater cardiac workload because of lack of familiarity and age mismatch (usually older men with a younger woman), with different activities and expectations.

By using our knowledge of MET equivalents in the clinical setting we can advise on sexual safety by comparing sexual intercourse to other activities. Some of the daily activities and MET equivalents are shown in Table 33.2.

Exercise testing
Using METs, sexual intercourse is equivalent to 3–4 minutes of the standard Bruce treadmill protocol. Where doubts exist about the safety of sexual intercourse, an exercise test can help guide decision-making. If a person can manage at least 4 minutes on the treadmill without significant symptoms, ECG evidence of ischemia, a fall in systolic blood pressure or dangerous arrhythmias, it will be safe to advise on sexual activity. If a patient is unable to perform an exercise test because of mobility problems, a pharmacological stress test should be utilized (e.g. dobutamine stress ECG). Advice on METs in the clinical setting, and relating this advice to sexual intercourse, should also include advice on avoiding stress, a heavy meal or excess alcohol consumption prior to sexual intercourse.

Cardiac risk
There is only a small risk of myocardial infarction associated with sex. The relative risk of a myocardial infarct during the 2 hours following sex is shown in Table 33.3. The baseline absolute risk of a myocardial infarction during normal daily life is low – one chance in a million per hour for a healthy adult and 10 chances in a million per hour for a patient with documented cardiac disease. Therefore, during the 2 hours after sex, the risk increases to 2.5 in a million for a healthy adult and 25 in a million for a patient with documented cardiac disease; but, importantly, there is no risk increase in those who are physically active (physically fit equals sexually fit). Coital sudden death is very rare.

Treating erectile dysfunction in patients with cardiovascular disease
The updated Princeton consensus guidelines are summarized in Table 33.1. It is recommended that all men with ED should undergo a full medical assessment (see Figure 33.1). Baseline physical activity needs to be established and cardiovascular risk graded as low, intermediate, or high. Most patients with low or intermediate cardiac risk can have their ED managed in the outpatient or primary care setting.
**Table 33.1 Risk from sexual activity in cardiovascular diseases: Second Princeton Consensus Conference**

<table>
<thead>
<tr>
<th>Low risk: typically implied by the ability to perform exercise of modest intensity without symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic and fewer than three major risk factors (excluding sex)</td>
</tr>
<tr>
<td>Major risk factors for cardiovascular disease include age, male sex, hypertension, diabetes mellitus, cigarette smoking, dyslipidemia, sedentary lifestyle, family history of premature coronary artery disease</td>
</tr>
<tr>
<td>Controlled hypertension</td>
</tr>
<tr>
<td>Beta-blockers and thiazide diuretics may predispose to erectile dysfunction</td>
</tr>
<tr>
<td>Mild, stable angina pectoris</td>
</tr>
<tr>
<td>Non-invasive evaluation recommended</td>
</tr>
<tr>
<td>Antianginal drug regimen may require modification</td>
</tr>
<tr>
<td>Post-revascularization and without residual ischemia</td>
</tr>
<tr>
<td>Exercise test may be beneficial to assess risk</td>
</tr>
<tr>
<td>Post-myocardial infarction (&gt;6–8 weeks), but asymptomatic and without exercise test-induced ischemia, or post-revascularization</td>
</tr>
<tr>
<td>If post-revascularization or no exercise test-induced ischemia, intercourse may be resumed 3–4 weeks after myocardial infarction</td>
</tr>
<tr>
<td>Mild valvular disease</td>
</tr>
<tr>
<td>May include selected patients with mild aortic stenosis</td>
</tr>
<tr>
<td>Left ventricular dysfunction (NYHA class II)</td>
</tr>
<tr>
<td>Most patients are low risk</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intermediate or indeterminate risk: evaluate to reclassify as high or low risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic and three or more risk factors for coronary artery disease (excluding sex)</td>
</tr>
<tr>
<td>Increased risk for acute myocardial infarction and death</td>
</tr>
<tr>
<td>Exercise test may be appropriate particularly in sedentary patients</td>
</tr>
<tr>
<td>Moderate, stable angina pectoris</td>
</tr>
<tr>
<td>Exercise test may clarify risk</td>
</tr>
<tr>
<td>Myocardial infarction within previous 2–6 weeks</td>
</tr>
<tr>
<td>Increased risk of ischemia, re-infarction, and malignant arrhythmias</td>
</tr>
<tr>
<td>Exercise test may clarify risk</td>
</tr>
<tr>
<td>Left ventricular dysfunction or congestive heart failure (NYHA class II)</td>
</tr>
<tr>
<td>Moderate risk of increased symptoms</td>
</tr>
<tr>
<td>Cardiovascular evaluation and rehabilitation may permit reclassification as low risk</td>
</tr>
<tr>
<td>Non-cardiac atherosclerotic sequelae (peripheral arterial disease, history of stroke, or transient ischemic attacks)</td>
</tr>
<tr>
<td>Increased risk of myocardial infarction</td>
</tr>
<tr>
<td>Cardiological evaluation should be considered</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>High risk: defer resumption of sexual activity until after cardiological assessment and treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unstable or refractory angina</td>
</tr>
<tr>
<td>Increased risk of myocardial infarction</td>
</tr>
<tr>
<td>Uncontrolled hypertension</td>
</tr>
<tr>
<td>Increased risk of acute cardiac and vascular events (e.g. stroke)</td>
</tr>
<tr>
<td>Congestive heart failure (NYHA class III, IV)</td>
</tr>
<tr>
<td>Increased risk of cardiac decompensation</td>
</tr>
<tr>
<td>Recent myocardial infarction (within 2 weeks)</td>
</tr>
<tr>
<td>Increased risk of re-infarction, cardiac rupture, or arrhythmias, but impact of complete revascularization on risk is unknown</td>
</tr>
<tr>
<td>High-risk arrhythmias</td>
</tr>
<tr>
<td>Rarely, malignant arrhythmias during sexual activity may cause sudden death</td>
</tr>
<tr>
<td>Risk is decreased by an implanted defibrillator or pacemaker</td>
</tr>
<tr>
<td>Obstructive hypertrophic cardiomyopathies</td>
</tr>
<tr>
<td>Cardiovascular risks of sexual activity are poorly defined</td>
</tr>
<tr>
<td>Cardiological evaluation (i.e., exercise testing and echocardiography) may guide patient management</td>
</tr>
<tr>
<td>Moderate-to-severe valve disease</td>
</tr>
<tr>
<td>Use vasoactive drugs with caution</td>
</tr>
</tbody>
</table>

NYHA, New York Heart Association.
Table 33.2 Metabolic equivalent of task units (METs) as a guide to relating daily activity to sexual activity

<table>
<thead>
<tr>
<th>Daily activity</th>
<th>METs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexual intercourse with established partner</td>
<td>2–3</td>
</tr>
<tr>
<td>Lower range (normal)</td>
<td>2–3</td>
</tr>
<tr>
<td>Lower range orgasm</td>
<td>3–4</td>
</tr>
<tr>
<td>Upper range (vigorous activity)</td>
<td>5–6</td>
</tr>
<tr>
<td>Lifting and carrying objects (9–20kg)</td>
<td>4–5</td>
</tr>
<tr>
<td>Walking 1.6 km (1 mile) on the level in 20 minutes</td>
<td>3–4</td>
</tr>
<tr>
<td>Golf</td>
<td>4–5</td>
</tr>
<tr>
<td>Gardening (digging)</td>
<td>3–5</td>
</tr>
<tr>
<td>Do-it-yourself, wall-papering, etc.</td>
<td>4–5</td>
</tr>
<tr>
<td>Light housework (e.g. ironing, polishing)</td>
<td>2–4</td>
</tr>
<tr>
<td>Heavy housework (e.g. making beds, scrubbing floors, cleaning windows)</td>
<td>3–6</td>
</tr>
</tbody>
</table>

Table 33.3 Relative risk of myocardial infarction during the 2 hours after sexual activity: physically fit equals sexually fit

<table>
<thead>
<tr>
<th>Patient type</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>2.5 (1.7–3.7)</td>
</tr>
<tr>
<td>Men</td>
<td>2.7 (1.8–4.0)</td>
</tr>
<tr>
<td>Women</td>
<td>1.3 (0.3–5.2)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>2.9 (1.3–6.5)</td>
</tr>
<tr>
<td>Sedentary life</td>
<td>3.0 (2.0–4.5)</td>
</tr>
<tr>
<td>Physically active</td>
<td>1.2 (0.4–3.7)</td>
</tr>
</tbody>
</table>

There is no evidence that treating ED in patients with cardiovascular disease increases cardiac risk; however, this is with the proviso that the patient is properly assessed and the couple or patient (self-stimulation may be the only form of sexual activity) are appropriately counseled. Oral drug therapy is the most widely used because of its acceptability and effectiveness, but all therapies have a place in management. The philosophy is always to be positive during what, for many men and their partners, is an uncertain time.

Phosphodiesterase type 5 inhibitors

Hemodynamically, phosphodiesterase (PED) type 5 inhibitors have mild nitrate-like actions (sildenafil was originally intended to be a drug for stable angina). Because PDE-5 is present in smooth muscle cells throughout the vasculature and the nitric oxide (NO)–cGMP pathway is involved in the regulation of blood pressure, PDE-5 inhibitors have a modest hypotensive action. In healthy men a single dose of sildenafil 100mg transiently lowered blood pressure by an average of 10/7mmHg, with a return to baseline at 6 hours post-dose. There was no effect on heart rate. Because NO is an important neurotransmitter throughout the vasculature and is involved in the regulation of vascular smooth muscle relaxation, a synergistic and clinically important interaction with oral or sublingual nitrates can occur and a profound decrease in blood pressure can result. The mechanism involves a combination of increased cGMP formation when nitrates activate guanylate cyclase and decreased breakdown of cGMP as a result of the action of PDE-5 inhibitors. The concomitant administration of PDE-5 inhibitors and nitrates is thus contraindicated and this recommendation also extends to other NO donors such as nicorandil. Clinical guidelines recommend that sublingual nitrates should be taken 12 hours after the PDE-5 inhibitors sildenafil and vardenafl; tadalafil, which has a longer half-life, ceases to react with nitrates only after 48 hours. Oral nitrates are not prognostically important drugs and they can therefore be discontinued and, if necessary, alternative agents substituted. After oral nitrate cessation, and provided there has been no clinical deterioration, PDE-5 inhibitors can be used safely. It is recommended that the time interval before the use of a PDE-5 inhibitor use is five half-lives, which equates to 5 days in the case of most popular once-daily oral nitrate agents.

Observations

The Princeton II guidelines emphasize the link between the ED and vascular disease and strongly recommend a cardiovascular risk assessment even when there are no cardiac symptoms. An exercise test will assess the functional ability of the patient but a normal exercise ECG does not rule out subclinical plaques, which may be vulnerable to rupture. The symptomatic cardiac patient should have his therapy optimized to allow for safe sexual activity. The cardiologist needs to be involved as part of a multidisciplinary approach, which might include the urologist, the family doctor, and a specialized nurse.

Due emphasis is given to lifestyle advice (increased exercise and weight loss) as well as drug therapy. There is reassurance concerning the cardiovascular safety of PDE-5 inhibitors providing that drug interactions are remembered, and there is no evidence that vacuum pumps, intracavernous injection therapy, or transurethral alprostadil are deleterious.

The Princeton Guidelines, by highlighting the link between ED and coronary artery disease, are intended to help to detect the cardiac patient before he has an event that will trigger risk factor reduction benefits. In addition they offer guidance on assessment and therapy in a positive and constructive way.
REFERENCES

34 Phosphodiesterase type 5 inhibitors: safety and adverse events

Konstantinos Hatzimouratidis and Dimitrios Hatzichristou

Introduction

Erectile dysfunction (ED) is a highly prevalent disease, as well as a major men’s sexual concern.1–2 The proportion of older people in the population increases, it has been estimated that the worldwide prevalence of ED will double from 152 million men in 1995 to 322 million men in 2025.4 Today, phosphodiesterase (PDE) type 5 inhibitors are considered the first-choice treatment for ED by both physicians and patients.4,5 The safety of these drugs is becoming more important since more than 30 million men are treated worldwide with a PDE-5 inhibitor, especially in the primary care setting. This chapter summarizes current knowledge on safety and adverse events of PDE-5 inhibitors, providing clinical guidance on essential topics related to drug interactions and contraindications.

Adverse events and discontinuation rates

The currently available PDE-5 inhibitors (sildenafil, tadalafil, and vardenafil) have been shown to be efficacious and safe treatment options for patients with ED. Being of the same class of drugs, they share common side-effects, although differences have been noticed in the reported frequency and severity of these symptoms; therefore an analysis follows for each of the three.

Sildenafil

Sildenafil was the first commercially available PDE-5 inhibitor, and its safety profile has been assessed in numerous studies.6–8 The most commonly reported treatment-related adverse events are headache, facial flushing, dyspepsia, dizziness, rhinitis, and abnormal vision (Table 34.1).9 Adverse events are typically transient and mild to moderate, and they are due to the vasodilatory effects of the medication; these include headache, flushing, and nasal congestion. Dyspepsia is probably secondary to relaxation of the smooth muscle of the gastroesophageal sphincter. Visual disturbances (blurred vision, flashing lights, blue haze, and change in color perception) occur as a result of weak inhibition of PDE-6 in the retina. They are coincident with peak plasma concentrations of sildenafil and are transient and fully reversible. None persisted 6 hours after taking sildenafil and are rarely a reason for discontinuing treatment.7 In this review including 5 fixed- and 6 flexible-dose trials, placebo patients were more likely to drop out than treatment patients from treatment-related adverse events (2% for sildenafil vs 2.3% for placebo, differences not statistically significant).

Long-term safety data from open-label extension studies revealed very low rates of treatment-emergent adverse events (see Table 34.1).7 However, this population differed from those of the pooled double-blind studies in that it was self-selected. Therefore, it is likely that the population included mostly men who had previously experienced a good response to sildenafil. Post-marketing case series reported a higher incidence of adverse events, especially for headache (9–39%), flushing (7–33%) and abnormal vision (5–11%).7 Patients may tolerate sildenafil differently based on existing comorbidities. Ischemic heart disease and hypertension are associated with higher incidence of discontinuation rates caused by adverse events than diabetes (3.6%, 2.3%, and 1.9% respectively).7

Multiple studies have demonstrated that sildenafil is well tolerated by elderly patients with ED, irrespective of comorbid conditions. Rates of serious adverse events and discontinuation of treatment owing to adverse events are similar between placebo and sildenafil groups.6–11 The safety profile of sildenafil remains unchanged in patients with spinal cord injury or depression treated with serotonin reuptake inhibitors.12,13

Tadalafil

The most frequent adverse events reported by patients on tadalafil were headache, flushing, nasopharyngitis, and back pain or myalgia (Table 34.2).14 These adverse events were primarily mild or moderate and generally self-limited over continuous use of the drug. Only few patients discontinued treatment in each of the treatment groups (1.3% for placebo, 1.6% for tadalafil 10mg, 3.2% for tadalafil 20mg), although the difference was significant between tadalafil and placebo (p=0.026). The long-term safety and tolerability of tadalafil assessed in a 24-month extension trial (all patients started at a dose of tadalafil 10mg but dose could be increased to 20mg or decreased to 5mg).15 No unexpected adverse event was recorded. Serious adverse events occurred in 8.6% of patients but no consistent pattern of serious adverse events was assessed as causally associated with tadalafil administration. The discontinuation rate because of adverse events was 6.3%,
Table 34.1 Drug-related adverse events and discontinuation rates associated with on-demand use of sildenafil

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>18 randomized, double-blind, placebo-controlled trials, lasting up to 6 months (fixed and flexible dose, n=5918)</th>
<th>Open-label, 4-year extension trial (3-year data, flexible dose, n=979)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Sildenafil</td>
</tr>
<tr>
<td></td>
<td>Sildenafil</td>
<td>Sildenafil</td>
</tr>
<tr>
<td>Headache</td>
<td>3.3%</td>
<td>14.6%</td>
</tr>
<tr>
<td>Flushing</td>
<td>1.9%</td>
<td>14.1%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>0.7%</td>
<td>6.2%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1.1%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>0.2%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Abnormal vision</td>
<td>0.3%</td>
<td>5.2%</td>
</tr>
<tr>
<td>Discontinuation as a result of treatment-related adverse events</td>
<td>2.3%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Table 34.2 Drug-related adverse events and discontinuation rates associated with on-demand use of tadalafil

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>11 randomized, double-blind, placebo-controlled, parallel studies lasting 12 weeks</th>
<th>Open-label, 24-month extension trial</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n=638)</td>
<td>Tadalafil 10mg (n=321) Tadalafil 20mg (n=1143)</td>
</tr>
<tr>
<td></td>
<td>Tadalafil (flexible dose) (n=1173)</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>5%</td>
<td>12%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>1%</td>
<td>7%</td>
</tr>
<tr>
<td>Back pain</td>
<td>2%</td>
<td>6%</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>4%</td>
<td>8%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>1%</td>
<td>5%</td>
</tr>
<tr>
<td>Flushing</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>Limb pain</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>Discontinuation as a result of treatment-related adverse events</td>
<td>1.3%</td>
<td>1.6%</td>
</tr>
</tbody>
</table>

while 3.1% of the patients discontinued as a result of adverse events that were assessed by the investigator as being possibly related to tadalafil.

Visual disturbances are very rare since tadalafil clinically lacks selectivity for PDE-6. Myalgia or back pain is a common adverse event related to tadalafil, in contrast to the other two PDE-5 inhibitors but its pathophysiology is poorly understood. Owing to the fact that tadalafil is also an inhibitor of PDE-11, an enzyme encountered also in the testis, safety concerns about sperm effects were raised. A study conducted in men older than 45 years revealed no effect on spermatogenesis or reproductive hormones after chronic administration of tadalafil (10mg and 20mg) for 6 months. Preliminary results indicate that tadalafil may acutely (1–2 hours after administration of a single 20mg dose) impair sperm motility in young, infertile patients. However, there are no data showing that this fact may be of any clinical significance.

Studies across different ethnic groups and various risk factors revealed the same pattern of adverse events and discontinuation rates, without statistically significant differences between groups. This was also the case in patients treated in tertiary care academic centers where more severe ED and ED-associated comorbidities are expected compared with patients treated in primary care centers. Finally, the safety pattern of tadalafil did not change when administered continuously (20mg, 3 times per week or 5–10mg daily) compared with on-demand use in general ED populations or in ED patients with diabetes mellitus.

Vardenafil

The most frequent adverse events reported by patients on vardenafil were headache, flushing, and rhinitis, consistent with the vasodilatory properties of PDE-5 inhibitors (Table 34.3).
Discontinuation rates because of treatment-emergent adverse events were similar to those for placebo (2% for placebo vs 3% for vardenafil). Treatment-emergent adverse events were generally of mild-to-moderate intensity and rapidly decreased during long-term treatment. Among patients receiving vardenafil 10mg group and 2% of patients in the vardenafil 20mg group discontinued treatment because of adverse events.

Visual disturbances are reported more rarely than with sildenafil. Serious adverse events were infrequent, reported by 1–5% of patients receiving vardenafil 5–20mg and 3–5% of placebo recipients in short-term studies and in 11% and 13% of patients receiving vardenafil 10mg and 20mg, respectively, in the 104-week study, but only one event (reduced visual acuity) was judged as possibly related to vardenafil treatment.

In the post-marketing surveillance study involving almost 30,000 patients in Germany, adverse events were reported by only 1.4% of men. The incidence of adverse events with vardenafil under ‘real-life’ conditions appears to be much lower than that seen in clinical trials. Similar results have been reported in other general ED populations, in aging men, in patients with diabetes mellitus, and in patients with spinal cord injury.

Cardiovascular safety

There is no evidence that treating ED with PDE-5 inhibitors increases cardiac risk. ED and vascular disease share the same risk factors and ED in otherwise asymptomatic men may be a marker of silent vascular disease, especially coronary artery disease. This has now been established to be the case and is discussed extensively in the second Princeton consensus.

Sildenafil

Clinical trials and post-marketing data of sildenafil demonstrated no increase in myocardial infarction rates either in patients who received these agents as part of double-blind, placebo-controlled trials or open-label studies, or compared with expected rates in aged-matched populations of men. Analysis of pooled data from more than 120 clinical trials found that sildenafil usage in men with ED did not increase the risk of myocardial infarction or cardiovascular death within 6 or 24 hours after intercourse, or overall. Overall, the rate per 100 patient-years of myocardial infarction or cardiovascular death in men treated with sildenafil was similar to that in men treated with placebo (0.91 vs 0.84) and was slightly lower in open-label and extension studies (0.56).

Sildenafil also has a strong overall safety profile in men with ED and comorbid cardiovascular disease. Pooled data from 37 double-blind, placebo-controlled trials of sildenafil showed similar adverse event profiles for the subset of men with comorbid cardiovascular disease and the overall ED population enrolled in these clinical trials. Except for facial flushing (vasodilatation), each type of treatment-related cardiovascular adverse event (e.g. palpitations, tachycardia) occurred in <1% of men, regardless of treatment assignment or comorbid condition. Similar results have been reported in prospective trials.

Sildenafil does not adversely affect total exercise time or time to ischemia during exercise testing in men with stable angina. In fact it may actually improve exercise tests. While sildenafil causes a modest decrease in blood pressure in both normal and hypertensive patients, it does not result in cardiac strain. Sildenafil does not alter cardiac contractility, cardiac output, or myocardial oxygen consumption, while it improves endothelial function.

Tadalafil

In clinical studies of tadalafil, the incidence of myocardial infarction was low and similar to that seen with placebo. Myocardial infarction rates in 35 controlled clinical trials were 0.26 per 100 patient-years in tadalafil-treated patients and 0.41 per 100 patient-years in placebo-treated patients. In 8 open-label studies, these rates were 0.36 and 0.33, respectively. These rates were no higher than the myocardial infarction rate of 0.6 per 100 patient-years reported for an age-standardized
population (men under 75 years of age). In all trials, the cardiac mortality rate was 0.12 per 100 patient-years compared with 0.26 per 100 patient-years for an age-standardized population.

The incidence of cardiovascular adverse events (including congestive heart failure, cerebrovascular events, hypotension, and arrhythmias) was low and similar to that seen with placebo. Observational studies confirmed this safety profile, reporting similar ischemic heart disease and myocardial infarction rates to those in the general male population. Finally, the incidence rates of myocardial infarction and cardiovascular treatment-emergent adverse events were similar to those with placebo even in cases of once-daily or 3 times per week dosing.

Daily tadalafil administration in healthy men resulted in blood pressure decreases similar to those seen with placebo administration. Single doses of 5mg and 10mg in men with coronary artery disease resulted in small decreases of blood pressure that were not associated with significant hypotensive symptoms. There is no evidence for QT prolongation induced by tadalafil. Tadalafil had no significant effect on global myocardial blood flow at rest, during adenosine infusion, or during dobutamine infusion. Compared with placebo, tadalafil significantly augmented myocardial blood flow during increased workload in normal regions, with a trend toward improving myocardial blood flow in poorly perfused regions. Chronic administration of tadalafil improves endothelial function in men with or without cardiovascular risk factors.

**Vardenafil**

Vardenafil is associated with a very low risk for myocardial infarction, similar to that seen with placebo. In double-blind and open-label clinical trials, myocardial infarction occurred in 0.1% of 793 placebo-treated patients compared with 1% of 1812 vardenafil-treated patients, with only 1 patient in each group sustaining a myocardial infarction. In this analysis, 1 placebo-treated patient had a stroke, while no vardenafil-treated patient had a stroke. Similarly, patients reporting angina or chest pain included 2 (0.3%) in the placebo group and 1 (<0.1%) in the vardenafil-treated group.

The incidence of cardiovascular adverse events in double-blind, long-term, open-label, and real-life studies was very low (≤0.1% for individual events) and similar to that with placebo. Only a few serious cardiovascular adverse events were reported but none was considered to be due to vardenafil. In a retrospective analysis of 17 clinical studies of vardenafil in men with ED, the incidence rates of drug-related dizziness was slightly higher in vardenafil-treated patients than in placebo-treated patients (1.5% vs 0.4%), but without additive effects by antihypertensive or alpha-blocker use.

Vardenafil had only small effects on corrected QT intervals that were not associated with absolute QT prolongation, and they are not considered clinically significant. There was no evidence of long-term cardiovascular safety concerns according to vital sign and electrocardiographic recordings during 2 years of treatment with vardenafil. Compared with placebo, vardenafil had no significant effect on mean total exercise time or time to first awareness of angina. Vardenafil 10mg (but not 20mg) significantly prolonged the time to ischemic threshold (i.e. ST-segment depression ≥1mm compared with baseline). As with the other two PDE-5 inhibitors, vardenafil also improves endothelial function.

**Phosphodiesterase type 5 inhibitors and antihypertensive medications**

All PDE-5 inhibitors share mild-to-moderate vasodilator effects, resulting in transient decreases in systolic and diastolic blood pressures in healthy volunteers. Since hypertension is a common risk factor in ED patients, it is important to determine if PDE-5 inhibitors potentiate the decreases in blood pressure achieved with different classes of antihypertensive agents.

The incidence of treatment-related adverse events for patients taking sildenafil and antihypertensive medications was similar to that for sildenafil-treated patients not taking any antihypertensive agent (34% vs 38%) in 18 double-blind, placebo-controlled studies. The number of antihypertensive medications taken from among the five classes (diuretic, beta-blocker, alpha-1-blocker, angiotensin converting enzyme inhibitor, and calcium-channel blocker) had no effect on the adverse event profile of sildenafil even among patients taking more than three different agents. Therefore, sildenafil is a well-tolerated treatment for ED in patients taking concomitant antihypertensive medication, including those on multi-drug regimens.

Tadalafil administration in patients receiving concomitant antihypertensive therapy may result in a reduction in blood pressure, which is, in general, mild and not likely to be of clinical concern. In the phase 3 studies, no statistically significant differences were observed between tadalafil and placebo in the mean changes in blood pressure from baseline in patients taking ≥2 antihypertensive agents. The incidence rates of cardiovascular events in six phase 3 trials were similar in tadalafil-treated patients (3.7%) and placebo-treated patients (4.8%). Hypotension or postural hypotension was not reported in any tadalafil-treated patient, compared with one report of each in the placebo-treated patients. Consequently, tadalafil is safe in patients receiving concomitant antihypertensive agents.

Vardenafil is associated with a low incidence of treatment-emergent adverse events (21.2%) and discontinuation rates (2.1%) compared with placebo (16.4% and 1%, respectively) in ED patients receiving antihypertensive agents. There were no significant changes in systolic and diastolic blood pressure or heart rate between the vardenafil and placebo groups. The average number of antihypertensives used per patient was 1.5 (range 1–4) in the vardenafil group and 1.4 (range 1–5) in the placebo group. Both the incidence of adverse events and the ability to maintain an erection were unaffected by stratification into distinct subsets according to the class of antihypertensive medication being received. Consequently, in hypertensive men treated with concomitant antihypertensive medication, vardenafil is well tolerated, and does not significantly affect blood pressure.

**Phosphodiesterase type 5 inhibitors and alpha-adrenergic antagonists**

Co-administration of PDE-5 inhibitors and alpha-adrenergic antagonists may result in an additive drop of blood pressure.
Non-arteritic anterior ischemic optic neuropathy

The non-arteritic type of anterior ischemic neuropathy is not due to inflammation of the arteries; rather, it results from transient poor circulation or loss of circulation in the capillaries of the optic nerve head, causing infarction of the anterior optic nerve. It is a rare disorder (the annual incidence is 2.3 to 10.3 per 100,000).\(^{70,71}\) The pathophysiology of non-arteritic anterior ischemic neuropathy (NAION) is controversial. It is postulated that decreased perfusion in the pial vasculature (the capillaries feeding the optic nerve head) results in hypoperfusion and ischemia of the optic nerve head. A vascular nature is suggested by the abrupt onset of symptoms typical of ischemia, the increased incidence in older age, and the strong association with vascular risk factors. NAION onset is typically characterized by sudden painless monocular visual loss that may progress over hours to weeks without any proven effective treatment.\(^{72-74}\)

A total of 196 post-marketing reports of NAION in patients using PDE-5 inhibitors (168 reports with sildenafil, 18 reports with tadalafil, and 10 reports with vardenafil) had been received by the US Food and Drug Administration (FDA) as of June, 2007. Thirty-six of these cases appear to be of the NAION subtype. In 26 cases, the loss of vision was described as continuing or permanent. Furthermore, five cases have been reported in Canada.\(^{72,73}\) There are 17 NAION case reports published in association with sildenafil and three in association with tadalafil.\(^{74}\) A few of the cases associated with sildenafil use and one case associated with tadalafil experienced temporary partial visual loss that became a fixed visual loss upon rechallenging. No case reports have been published in association with vardenafil usage.

Based on the similar risk profiles for both NAION and ED, it is not unexpected to observe NAION cases in men with ED.

Establishing a causal relationship between NAION and a specific risk factor (including the use of a particular medication) is problematic since most patients with NAION have one or more concurrent systemic or local risk factors that place them at risk for optic head ischemia. On 8 July, 2005, the FDA approved updated labeling for all three PDE-5 inhibitors, reflecting current knowledge of the possible association with NAION. At this time, it is not possible to determine whether PDE-5 inhibitors were the cause of the loss of eyesight or whether the problem is related to other factors such as high blood pressure or diabetes, or to a combination of these problems. The FDA advises patients to stop taking these medicines and call a doctor or healthcare provider right away if they experience a sudden or decreased vision loss in one or both eyes. Patients taking or considering taking these products should inform their healthcare professionals if they have ever had severe loss of vision, which might reflect a prior episode of NAION. Such patients are at an increased risk of developing NAION again and PDE-5 inhibitors should not be considered until possible risk factors are optimized. Aspirin is the only medication that shows some potential benefit in reducing the frequency of second eye involvement in patients with NAION.\(^{75}\) Therefore, a reasonable and informed consent should be provided by the clinician to patients regarding the possible but low risk of NAION in association with PDE-5 inhibitors.\(^{75}\)

Contraindications

Consistent with the effects of PDE-5 inhibition on the nitric oxide (NO)–cGMP pathway, all PDE-5 inhibitors may potentiate the hypotensive effects of nitrates. Therefore, the administration of all PDE-5 inhibitors is contraindicated in patients who are using any form of organic nitrates, either regularly or intermittently. Patients with known hereditary degenerative retinal disorders, including retinitis pigmentosa, were not included in clinical trials, and PDE-5 inhibitor use in these patients is not recommended.

Other precautions

Several precautions exist in patient subpopulations and as a result of drug interactions.\(^{76-78}\) Renal insufficiency alters the pharmacokinetics of PDE-5 inhibitors, increasing both the area under the curve (AUC) and the maximum plasma concentration. A starting oral dose of 25mg should be considered for sildenafil in patients with severe renal insufficiency. No modifications are necessary in patients with mild or moderate renal insufficiency. The dose of tadalafil should be limited to 5mg not more than once daily in patients with severe renal insufficiency or end-stage renal disease. A starting dose of 5mg not more than once daily is recommended for patients with moderate renal insufficiency; the maximum recommended dose is 10mg not more than once in every 48 hours. No dose adjustment is required in patients with mild renal insufficiency. In patients with moderate or severe renal insufficiency, the AUC of vardenafil...
was 20–30% higher than in normal subjects. Vardenafil pharmacokinetics have not been evaluated in patients requiring renal dialysis.

In patients with hepatic cirrhosis (Child–Pugh score A and B), a starting oral dose of 25mg should be considered for sildenafil. Tadalafil dose should not exceed 10mg in these patients, and use in patients with severe hepatic impairment (Child–Pugh score C), is not recommended. Finally, a starting dose of 5mg of vardenafil is recommended for patients with moderate hepatic impairment, and the maximum dose should not exceed 10mg. Vardenafil has not been evaluated in patients with severe hepatic impairment.

Drug interactions may play a significant role in the safety profile of PDE-5 inhibitors. Besides precautions already reported, Table 34.4 summarizes effects of PDE-5 inhibitors on other drugs. Physicians must be aware of these effects, since dose and treatment modifications may be necessary. The safety of PDE-5 inhibitors in patients with bleeding disorders and patients with active peptic ulceration is not documented.

Therefore, they should be administered to these patients only after careful benefit–risk assessment and with caution. Co-administration with aspirin does not prolong bleeding time, relative to aspirin alone.

Both alcohol and PDE-5 inhibitors act as mild vasodilators. When mild vasodilators are taken in combination, blood-pressure-lowering effects of each individual compound may be increased. Regular alcohol consumption does not alter pharmacokinetics of PDE-5 inhibitors. However, substantial consumption of alcohol (e.g., 5 units or greater) in combination with a PDE-5 inhibitor can increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness, and headache.

PDE-5 inhibitors should be used with caution in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis, or Peyronie’s disease), or in patients who have conditions that may predispose them to priapism (such as sickle cell anemia, multiple myeloma, or leukemia).

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### Table 34.4 Effects of other drugs on phosphodiesterase (PDE) type 5 inhibitors

<table>
<thead>
<tr>
<th>Study drug (dose studied for each PDE-5 inhibitor)</th>
<th>Mechanism of interaction</th>
<th>Sildenafil</th>
<th>Tadalafil</th>
<th>Vardenafil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cimetidine (800mg, N/A, 400mg bd)</td>
<td>Non-specific CYP inhibitor</td>
<td>56% increase in plasma concentrations (50mg)</td>
<td>N/A (nizatidine – another H₂ antagonist – has no effect)</td>
<td>No effect</td>
</tr>
<tr>
<td>Erythromycin (500mg tid, N/A, 500mg bd)</td>
<td>CYP3A4 inhibitor</td>
<td>182% increase in AUC (100mg)</td>
<td>N/A (would probably increase tadalafil exposure)</td>
<td>Three-fold increase in Cmax, four-fold increase in AUC</td>
</tr>
<tr>
<td>Ritonavir (500mg bd, 200mg bd, 800mg tid)</td>
<td>P450 inhibitor</td>
<td>300% increase in Cmax (100mg), 1000% increase in AUC (100mg)</td>
<td>No change in Cmax, 124% increase in AUC</td>
<td>13-fold increase in Cmax, 49-fold increase in AUC</td>
</tr>
<tr>
<td>Saquinavir (1200mg tid, N/A, N/A)</td>
<td>CYP3A4 inhibitor</td>
<td>140% increase in Cmax (100mg), 210% increase in AUC (100mg)</td>
<td>N/A (expected to increase tadalafil exposure)</td>
<td>N/A (expected to increase vardenafil exposure)</td>
</tr>
<tr>
<td>Indinavir (N/A, N/A, 800mg tid)</td>
<td></td>
<td>N/A (expected to increase sildenafil exposure)</td>
<td>N/A (expected to increase tadalafil exposure)</td>
<td>Seven-fold increase in Cmax, 16-fold increase in AUC</td>
</tr>
<tr>
<td>Ketoconazole (N/A, 400mg daily, 200mg daily)</td>
<td>CYP3A4 inhibitor (strong)</td>
<td>N/A (expected to increase sildenafil exposure)</td>
<td>22% increase in Cmax (20mg), 15% increase in Cmax (10mg), 312% increase in AUC (20mg), 107% increase in AUC (10mg)</td>
<td>4-fold increase in Cmax, 10-fold increase in AUC</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>CYP3A4 inhibitor (strong)</td>
<td>N/A (expected to increase sildenafil exposure)</td>
<td>N/A (would probably increase tadalafil exposure)</td>
<td>N/A (would probably increase vardenafil exposure)</td>
</tr>
<tr>
<td>Grapefruit</td>
<td>CYP3A4 inhibitor (weak)</td>
<td>N/A (may give rise to modest increases in plasma levels)</td>
<td>N/A (would probably increase tadalafil exposure)</td>
<td>N/A (would probably increase vardenafil exposure)</td>
</tr>
<tr>
<td>Rifampin (N/A, 600mg daily, N/A)</td>
<td>CYP3A4 inducer</td>
<td>N/A (expected to decrease sildenafil exposure)</td>
<td>46% decrease in Cmax (10mg), 88% decrease in AUC (10mg)</td>
<td>N/A (expected to decrease vardenafil exposure)</td>
</tr>
</tbody>
</table>

CYP, cytochrome P450 isoenzyme; AUC, area under the curve; Cmax, maximum plasma concentration.
There have been rare reports of prolonged erections for more than 4 hours and priapism (painful erections lasting longer than 6 hours) for this class of compounds. The safety and efficacy of combinations of PDE-5 inhibitors with other treatments for ED have not been studied in pre-marketing trials. However, there are data in the literature supporting combination of PDE-5 inhibitors with intracavernosal injections in non-responders to PDE-5 inhibitors alone. Such combinations may increase side-effects and they are not recommended in everyday clinical practice.

### Summary

Numerous clinical trials and post-marketing studies have established that PDE-5 inhibitors have an excellent overall safety profile. Adverse events are typically transient, mild-to-moderate in severity, and self-limiting with continuous use. Despite early concerns, the cardiovascular safety of PDE-5 inhibitors is also excellent with the incidence rates of cardiovascular adverse events being similar to those with placebo. Furthermore, recent data show that PDE-5 inhibitors may actually have a cardioprotective role. However, certain limitations and precautions exist. Physicians must be aware of these in order to treat ED patients safely and effectively.

### REFERENCES


31. van Ahlen H, Wahle K, Kupper W, et al. Safety and efficacy of vardenafil, a selective phosphodiesterase 5 inhibitor, in patients...

32. Mirone V, Palmieri A, Cucinotta D, et al. Flexible-dose vardenafil in a community-based population of men affected by erectile dys-


49. Klomer RA, Jackson G, Hutter AM, et al. Cardiovascular safety update of Tadalafil: retrospective analysis of data from placebo-controlled and open-label clinical trials of Tadalafil with as needed, three-times-
per-week or once-a-day dosing. Am J Cardiol 2006; 97: 1778–84.

50. Klomer RA, Mitchell M, Emmick JT. Cardiovascular effects of tada-


lafil improves endothelial function in men with increased cardio-

55. Carson CC, 3rd. Cardiac safety in clinical trials of phosphodi-
esterase 5 inhibitors. Am J Cardiol 2005; 96: 37M–41M.


57. Morganroth J, Ilison BE, Shaddinger BC, et al. Evaluation of varden-


59. Jackson G. Hemodynamic and exercise effects of phosphodi-


68. Giuliano F, Kaplan SA, Cabanis MJ, et al. Hemodynamic interac-
tion study between the alpha1-blocker alfuzosin and the phos-

69. Auerbach SM, Gittelman M, Mazzu A, et al. Simultaneous admin-
istration of vardenafil and tamsulosin does not induce clinically significant hypotension in patients with benign prostate hyperpla-

70. Hattenhauer MG, Leavitt JA, Hodge DO, et al. Incidence of nonarter-


72. Hatzichristou D. Phosphodiesterase 5 inhibitors and nonarteritic anterior ischemic optic neuropathy (NAION): coincidence or cau-

73. Bella AJ, Brant WO, Lue TF, et al. Non-arteritic anterior ischemic optic neuropathy (NAION) and phosphodiesterase type-5 inhibi-


75. Salomon O, Huna-Baron R, Steinberg DM, et al. Role of aspirin in reducing the frequency of second eye involvement in patients with
35 Diagnosis and treatment of hypogonadism

Mathew Oommen, Levent Gurkan, Allen D Seftel, and Wayne JG Hellstrom

Introduction

As men go beyond the fourth decade of life, there is a gradual decrease in serum testosterone levels. The US Food and Drug Administration (FDA) estimates that 4–5 million men in the USA suffer from true hypogonadism, with only 5% of these men actually being treated. Other sources estimate the range of hypogonadism in men above 40 years of age to be between 6.0% and 43.7%.1

Hypogonadism can be due to testicular dysfunction (primary testicular failure, primary hypogonadism, hypergonadotropic hypogonadism) or to central, hypothalamic–pituitary causes, which lead to hypergonadotropic hypogonadism (secondary hypogonadism). Primary testicular failure can be a result of the aging process but can also be caused by chemotherapy, radiation therapy, congenital defects, and genetic disorders, such as Klinefelter’s syndrome. Secondary hypogonadism is characterized by decreased luteinizing hormone (LH) production in the anterior pituitary. In addition to aging, known causes include pituitary tumors, surgery, radiation, infections, trauma, inflammation, bleeding, genetic disorders, nutritional deficiency, and hemochromatosis. Secondary hypogonadism may be associated with syndromes known as Kallmann’s, Prader–Willi, and Laurence–Moon–Biedl.

While hypogonadism is defined as a low total serum testosterone, symptomatic hypogonadism is characterized by low total serum testosterone together with clinical symptoms and signs. Symptoms include:

- sexual dysfunction, such as reduced libido, erectile dysfunction (ED), diminished penile sensation, and difficulty attaining orgasm, as well as diminished ejaculate with orgasm;
- reduced energy, vitality, or stamina;
- depressed mood or diminished sense of well-being;
- increased irritability;
- difficulty concentrating and other cognitive problems; and
- hot flashes in some cases of acute onset.

Many authorities have supported the position that symptomatic hypogonadism is a more realistic representation of the true hypogonadal state and thus look for a low serum testosterone level combined with one or more of the symptoms noted above to confirm the diagnosis of true hypogonadism.

The prevalence of hypogonadal symptoms was demonstrated by a Swedish survey of men aged 55–75 years, in which most subjects reported some symptoms of hypogonadism, regardless of their testosterone levels.2 Signs of hypogonadism include anemia, muscle wasting (sarcopenia), reduced bone mass or bone mineral density, abdominal adiposity, and oligospermia or azoospermia.

Frequently, the effects of age-related hypogonadism and effective treatment modalities are not even discussed with patients, owing to a lack of comfort in discussing sexual issues by both patients and their primary care providers. Discussing the symptoms and evaluating the signs of age-related hypogonadism openly and aggressively helps to change patients’ perspective that certain conditions are meant to be accepted as part of the aging process.

Diagnosis

Diagnosing age-related hypogonadism is not always a straightforward process. Frequently, hypogonadism is a diagnosis of exclusion (physicians arrive at the diagnosis only after eliminating all other possibilities) because the symptoms are rather vague and are of gradual onset. Further, there is no absolute consensus on what laboratory threshold values and other factors should be included in the formal definition of hypogonadism. Current models suggest using a combination of patient history, questionnaire, physical examination, and specific laboratory values.

Patient history

Often, questions dealing with family (relatives with hypogonadism), social history (smoking, heavy alcohol consumption), medical history (history of depression, diabetes, hypothyroidism), sexual history (changes in sexual practices, ED, and desire), and changes in sleep and exercise patterns can direct a physician to an easy diagnosis. There is general consensus that the diagnosis of hypogonadism must be not only on the basis of certain signs and symptoms (Table 35.1) but also on the basis of low serum testosterone levels.

Questionnaires used in the diagnosis of hypogonadism

Owing to the costly nature of laboratory tests, lack of defined coverage by insurance companies, and the uncertainties of
standard laboratory assays, there has been a debate as to whether other modalities besides a measurement of serum testosterone can be used to make a diagnosis of hypogonadism, especially in the growing population of elderly males. The use of relatively non-invasive and cost-effective questionnaires is becoming more accepted. When evaluated for specificity and sensitivity, current models such as the St Louis University Androgen Deficiency in Aging Males (ADAM) questionnaire are highly sensitive but not very specific for the diagnosis of hypogonadism. However, surveys using some of the ADAM questions may guide the clinician in following the patient response to treatment.

The ADAM questionnaire asks the following questions. The response is considered positive if the answer is yes to question 1 or question 7, or yes to at least three other questions.

1. Do you have a decrease in libido (sex drive)?
2. Do you have a lack of energy?
3. Do you have a decrease in strength and/or endurance?
4. Have you lost height?
5. Have you noticed a decreased enjoyment of life?
6. Are you sad and/or grumpy?
7. Are your erections less strong?
8. Have you noted a recent deterioration in your ability to play sports?
9. Are you falling asleep after dinner?
10. Has there been a recent deterioration in your work performance?

It is generally recognized that questionnaires are at the very best an adjunct to, but not a replacement for serum testosterone measurements. As these types of questions and surveys evolve, the level of specificity will also improve, which, in turn, may make them a more integral part in the diagnosis of hypogonadism.

**Physical examination**

A thorough but focused physical examination needs to be performed when evaluating a patient for hypogonadism. Particular attention is directed to secondary sexual characteristics, gynecomastia, muscle atrophy, changes in body fat composition, and testicular atrophy. Examination of the penis and a digital rectal examination is also mandatory.

**Laboratory tests**

Assessing the prevalence of hypogonadism is difficult because of the inconsistencies regarding which laboratory values are used to define hypogonadism. The use of total testosterone, bioactive testosterone (not bound to sex hormone-binding globulin) or free testosterone (not bound to sex hormone-binding globulin or albumin) in various studies makes pooling data from many studies difficult and inaccurate. Another issue is that symptoms may manifest themselves at varying levels of testosterone in different patients. One study showed that testosterone levels that elicited symptoms in an individual patient were reproducible but the exact concentration that elicited symptoms varied between patients.

According to the Second International Consultation on Erectile Dysfunction of the World Health Organization (WHO), a serum testosterone level should be obtained between 8.00am and 11.00am, when testosterone levels typically peak in healthy young men. The 25th percentile was 251ng/dl for healthy men aged 40–49 years, 216ng/dl for ages 50–59, 196ng/dl for ages 60–69, and 156ng/dl for ages 70–79. Corresponding 2.5th percentile values for free testosterone were 5.3ng/ml, 4.2ng/ml, 3.7ng/ml and 2.2ng/dl, respectively, and corresponding values for bioavailable testosterone were 99.7ng/ml, 79.8ng/ml, 69.7ng/ml, and 41.8ng/dl, respectively.

Finally, the exact values and methods of obtaining the results vary between laboratories. For instance, one recent study showed that not only did assay types vary between laboratories but even reference values for low testosterone (130–450ng/dl) and high testosterone (486–1593ng/dl) had discrepancies. In the previously mentioned study, 23 of the 25 laboratory directors said they would welcome the establishment of uniform standards that were clinically relevant. A recent study has shown that analysis of saliva samples for testosterone may yield comparable results to serum testosterone analysis in the diagnosis of hypogonadism. Regardless, more studies in this hot area of research are necessary before it can be considered as part of a standardized method for diagnosis of hypogonadism.

**Treatment**

Testosterone supplementation in hypogonadal men restores testosterone levels and improves secondary sexual characteristics, sexual function, sense of well-being, muscle mass and strength, and bone mineral density. Currently, there are many formulations of testosterone with varying advantages and disadvantages (Table 35.2).

**Suggested regimens of replacement therapy**

Suggested regimens of testosterone replacement therapy include:

- testosterone enanthate or cypionate, 75–100mg by intramuscular injection weekly or 150–200mg administered every 2 weeks;
- testosterone patch, non-genital, one or two 5mg patches applied nightly over non-pressure-bearing sites such as the back, chest, or upper arm;
• testosterone gel, 5–10mg applied daily to dry intact skin of the upper arm, back or chest; and
• buccal testosterone, 30mg patch applied twice daily to buccal mucosa.

Intramuscular preparations
Intramuscular injections such as testosterone cypionate and enanthate are esterified compounds that are dissolved in oil-based solutions. They can be given in varying doses ranging from 75mg to 400mg depending on the frequency of injections (75–100mg weekly, 150–200mg every 2 weeks, 300–400mg every 3 weeks). Doses higher than 400mg have not been demonstrated to lengthen the eugonadal period. One drawback is the frequency of injections, which may be unappealing to both physicians and patients.

For patients who prefer longer intervals between injections, testosterone undecanoate in oil is being used in Europe (1000mg every 6–12 weeks). However, patients must be willing to tolerate a slightly more painful, larger volume injection. A preparation currently undergoing trials in the USA is testosterone undecanoate in castor oil, which may last as long as 14 weeks after an initial 6-week loading dose.

Oral preparations
Though still prescribed by some clinicians, most authorities do not recommend 17-methyl testosterone in tablet form, owing to known changes in liver function tests and the need for relatively large doses. However, capsules that contain testosterone undecanoate in oil are available in Europe and Canada and are given in a twice- or three-times-daily dosing regimen.

Gels
Testosterone gels are applied to the skin in varying doses ranging from 5mg to 10mg daily. These preparations allow for steady states of testosterone and cause fewer adverse reactions at application sites. A drawback is the potential risk of testosterone transfer via skin contact to the partner or children.

Buccal patches
Buccal testosterone comes as a tablet-shaped patch, which is applied to the upper gum. It is a 30mg controlled-release tablet, which is applied every 12 hours. It has been shown to have good results in attaining eugonadal serum levels. However, drawbacks include irritation at the gum line and a twice-daily dosing schedule.

Transdermal patches
Current transdermal routes include daily patches that can be placed on the appendages or torso as well as scrotal patches. They have been shown to provide an adequate clinical response and appropriately increase serum testosterone levels. The most common complaint is irritation at the site of patch placement. The scrotal patch also increases levels of dihydrotestosterone secondary to high 5-alpha-reductase activity in scrotal skin. Another issue for some patients is the need for constant shaving of the scrotal skin for better adherence.

Monitoring of men receiving testosterone therapy
The patient should be initially evaluated 3 months after treatment starts and then annually to assess whether symptoms have responded to treatment and whether the patient is suffering any adverse effects.

1. Obtain testosterone levels 2–3 months after initiation of testosterone therapy. Therapy should aim to raise serum testosterone to within the normal range.
2. Check hematocrit at baseline, at 3 months, and then annually. If hematocrit is 54% or greater, stop therapy until hematocrit decreases to a safe level. The clinician must evaluate the patient for hypoxia and sleep apnea, and then may reinstate therapy at a reduced dose.
3. Measure bone mineral density of lumbar spine or femoral neck after 1–2 years of testosterone therapy in hypogonadal men with osteoporosis or a history of traumatic fracture, consistent with the regional standard of care.
4. Perform a digital rectal examination and check the prostate-specific antigen (PSA) level before treatment (at baseline), at 3 months, and then in accordance with guidelines for prostate cancer screening depending on the age and race of the patient. One study showed that parenteral testosterone replacement therapy in older hypogonadal men increased the serum PSA level by a mean of 0.96ng/ml over a mean treatment duration of 30.2 months.13

5. Obtain urological consultation if there is:
   - an increase in serum PSA concentration of 1.4ng/ml or greater within any 12-month period of treatment;
   - PSA velocity of >0.4ng/ml/year using the PSA levels after 6 months of testosterone administration as the reference (only applicable if PSA data are available for a period exceeding 2 years);
   - any prostatic anomaly on digital rectal examination;
   - AUA or American Urological Association prostate symptom score or International Prostate Symptom Score of 19 or more.

6. Evaluate formulation-specific adverse effects at each visit:
   - buccal testosterone tablets – enquire about alterations in taste and examine the gums and oral mucosa for irritation;
   - injectable testosterone – ask about fluctuations in mood or libido and pain at the injection site;
   - testosterone patches – examine for skin reaction at the injection site;
   - testosterone gels – advise patients to cover the application sites with a shirt and wash the skin with soap and water before having skin-to-skin contact, because testosterone gels leave a testosterone residue on the skin that can be transferred to a woman or child who might come in close contact; serum testosterone levels are maintained when the application site is washed 4–6 hours after application of the testosterone gel.

Contraindications to testosterone therapy

Treatment with testosterone is effective for the aging hypogonadal male. However, care must be taken during the initial screening and subsequent treatment regimen to assure that the patient does not have or develop conditions that would contraindicate initiating or continuing therapy. Conditions in which testosterone should not be administered include prostate cancer, breast cancer, prostate nodule without biopsy-confirmed histology, elevated PSA without work-up, erythrocytosis (hematocrit >50%), severe lower urinary tract symptoms associated with benign prostatic hypertrophy, and unstable severe congestive heart failure (New York Heart Association class III or IV).2 Prostate and breast cancers are usually hormone-dependent initially and may be stimulated with any form of testosterone therapy. In a similar fashion, benign prostatic tissue also responds to testosterone therapy. A thorough prostate evaluation needs to be performed prior to initiation of replacement therapy.

Adverse effects of testosterone therapy

The adverse effects of testosterone administration must be discussed with any patient contemplating replacement therapy.2

Adverse events for which there is evidence of association with testosterone administration

Patients should be notified that conditions such as increased acne, decrease in sperm production, possible decreased fertility rates, and elevations in the red blood cell count are possible. There should also be a discussion about the increased likelihood of detecting subclinical prostate cancer and the growth of hormone-sensitive metastatic prostate cancer.

Less common adverse events

Patients should be notified of the remote possibility of side-effects such as gynecomastia, initiation of male pattern baldness, and worsening of obstructive sleep apnea.

Medication-specific adverse effects

When the physician and patient are deciding on a form of testosterone therapy, formulation-specific effects should be discussed. For instance, oral methyltestosterone, if used, can damage the liver. Subcutaneous pellets can be extruded from the skin. Intramuscular injections of testosterone can cause problems such as fluctuations in mood, pain at the injection site, and excessive erythrocytosis. Transdermal testosterone patches can cause localized skin reactions. Transdermal testosterone gels and creams can potentially be absorbed by others via skin contact. Buccal testosterone patches can interfere with taste sensations and cause gum irritation.

Conclusion

By choosing appropriate formulations of testosterone based on factors such as ease of use, cost of medication, dosing interval, preferred method of administration, and side-effect profile, the treatment of hypogonadism can improve the quality of life for this greatly under-served patient population. The diagnosis and treatment of hypogonadism is continuing to evolve as newer detection methods and medication formulations become available.

REFERENCES

Central nervous system agents for the treatment of erectile dysfunction

Julita Mir and Ricardo Munárriz

Introduction

Although the central mechanisms involved in the regulation of erectile physiology are not completely understood, recent advances have allowed the development of promising central acting drugs. This chapter reviews the available data on apomorphine and melanocortins.

Central mechanism of penile erections

Penile erections are elicited by local sensory stimulation of the genital organs and by central psychogenic stimuli received by or generated within the brain.1–2 Recently, specific regions of the brain (inferior temporal cortex, right insula, right inferior frontal cortex, and left anterior cingulated cortex) activated by visual evoked sexual arousal have been identified by positron emission tomography.3 The medial preoptic area (MPOA) and the paraventricular nucleus (PVN) within the hypothalamus appear to integrate visual (occipital area), tactile (thalamus), olfactory (rhinencephalon), and imaginative (limbic system) input and send neural projections to the lumbosacral spinal cord through oxytocinergic pathways.4–5 More specifically, the MPOA integrates sensory stimuli from higher brain centers with sexual motivation and copulatory behavior,6 while the PVN plays a role in the erectile and ejaculatory responses.7–8 Dopamine and oxytocin are thought to play important roles in mediating the pre-erectile response in the MPOA and the PVN, respectively.9

Electrostimulation of the PVN induces erections, while damage of the nucleus disrupts the dopamine receptor mediated erectile responses.5,8 In addition, systemic dopamine receptor agonist or direct administration into the PVN induces penile erections while administration of dopamine receptor antagonist prevents erectile responses.10–12 These observations suggest that the PVN plays a critical role in the dopaminergic control of penile erections. There are five subtypes of dopaminergic receptors which have been classified into D1-like (D1 and 5) and D2-like (D2–4) receptors. The latter group is thought to be mainly responsible for erectile responses.10,11 D4 receptor agonists elicit penile erectile responses while D2 receptor stimulation is responsible for the emetic effects of dopaminergic drugs (Table 36.1).14

The PVN is also regulated by adrenocorticotropic hormone (ACTH) and alpha-melanocyte stimulating hormone (alpha-MSH). These melanocortin peptides can stimulate penile erections after intra- or paraventricular administration even after lesion of the nucleus, which suggests that ACTH may elicit penile erections through non-dopaminergic mechanisms.3,15,16 Interestingly, intrathecal administration of melanotan II (MT-II) was more effective in eliciting a penile erection than central (ventricles) administration, which suggests melanocortins modulate penile erections at the level of the spinal cord.17 Although melanocortin receptor type 4 (MC-4R) is expressed in the nerve fibers and nerve endings in the penis, intracavernosal administration of melanocortins (THIQ 1, 2, 3, 4 tetrahydroisoquinoline), MT-II did not change intracavernosal pressures.18

The melanocortin system includes melanocortin peptides, melanocortin receptors, melanocortin antagonists, and two ancillary proteins (mahogany and syndecan-3); it is involved in a variety of regulatory functions that include skin pigmentation, steroidogenesis, satiety, analgesia, immunomodulation, energy and temperature homeostasis, and cardiovascular, neuromuscular, and sexual function. There are five melanocortin receptors (MCRs), which are G protein-coupled and linked to cAMP generation. MCR type 1 (MC-1R) is primarily found in melanocytes where skin pigmentation is modulated by alpha-MSH.19 MCR type 2 (MC-2R) is expressed in the adipose tissue and the adrenal gland, where it modulates steroidogenesis under the influence of ACTH. MC-4R is involved in sexual function and adipose homeostasis and satiety (see Table 36.1). Agouti and agouti-related protein are natural melanocortin antagonists that play a role in appetite, obesity, and maybe in sexual function.

On the other hand, the nucleus paragigantocellularis (nPGi) in the brain stem exerts an inhibitory effect on sexual arousal.20 Nerves from the nPGi project to sacral segments of the spinal cord and release serotonin. This has been postulated as the reason why specific serotonin reuptake inhibitors (SSRIs) depress sexual function, more specifically delay or block ejaculation. Therefore, premature ejaculation has been successfully managed with SSRIs. The locus caeruleus also exerts inhibitory input via sympathetic nerves that interface with hypothalamic nuclei as well as with the spinal cord. Withdrawal of sympathetic input because of suppressed activity of the locus caeruleus during rapid eye movement sleep is thought to lead to episodes of nocturnal penile tumescence.21–22 The pudendal
nerve, which is the afferent limb for reflexogenic erections, collects somatic sensation from the genital skin. The autonomic nerve fibers that arise from the sacral parasympathetic center (spinal cord levels S2–S4) make up the efferent limb for this reflex, innervating the penile smooth muscle. Reflexogenic and psychogenic erectile mechanisms probably act synergistically in the control of penile erection.1,23–29

### Apomorphine in sexual function

Apomorphine, a non-selective dopamine receptor agonist, is the first central-acting drug approved in Europe (2001) for the management of erectile dysfunction (ED) (Table 36.2).30 Only after sexual stimulation, apomorphine can stimulate D2 receptors since the PVN integrates sensory and imaginative input. Stimulation of D2 receptors increases oxytocinergic neural signaling, which stimulates sacral spinal centers, resulting in increased parasympathetic stimulation and penile erections.

### Efficacy

Over 5000 men worldwide have received apomorphine SL (sublingual) in clinical trials. The first three phase 3 crossover studies (n=854; 2mg and 4mg doses) were conducted in men with mild (25.9%), moderate [International Index of Erectile Function (IIEF) 11–16; 36.8%), and severe (IIEF <10; 37.3%) ED.31 However, the majority of patients (74.1%) had moderate-to-severe ED. The following comorbidities were reported in these studies: hypertension (31%), coronary artery disease (16%), dyslipidemia (16%), diabetes (16%), benign prostatic hyperplasia (16%), alcohol use (63%), and smoking (16%). Combined data from these three crossover studies reported 54.6% and 45.6% successful attempts in attaining erections sufficient for intercourse for the 4mg and 2mg dose groups, respectively, compared with baseline (26.8%) and placebo (33.8%). Interestingly, partner’s responses were very similar to patient’s reports (54% and 46% for the 4mg and 2mg doses, respectively; concordance of 98%). Ability to have intercourse for the 4mg and 2mg dose groups were 50.6% and 41.5%, respectively, compared with baseline (25.7%) and placebo (31%).31

Long-term studies (n=135; 6 months) reported rates of successful erections (erections firm enough for intercourse) in 82.9–91.6% of all attempts. A more recent study by Kongkanand et al. reported improvements in erectile function (from 15.9 to 20.4), intercourse satisfaction (from 7.7 to 9.9), and orgasmic domains (from 6.8 to 7.5) in the IIEF.32

### Onset of action

Data from the first three phase 3 crossover trials show median times to erection of 17.5 and 16.4 minutes for the 2mg and 4mg doses, respectively, for all men achieving erections sufficient for intercourse. However, the time to erection in the placebo group was 15 minutes. Thus, there was no significant change in the timing of sexual response in comparison with placebo.

### Tolerability and safety

Several clinical trials have documented the safety of apomorphine SL in ED patients with mild-to-moderate adverse events.33–37 The most common reported adverse events were nausea, headache and dizziness. Nausea was reported in 2.1% and 20.4% of men who took the 2mg and 4mg doses, respectively, in the three first crossover studies. However, nausea was reported as mild in the majority of patients (1.2% and 12.2% for the 2mg and 4mg doses, respectively) and rarely

---

**Table 36.1 Receptor-binding affinities of apomorphine for dopamine receptor subtypes**

<table>
<thead>
<tr>
<th>Kᵢ (nM)</th>
<th>D1-like receptors</th>
<th>D2-like receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>D1</td>
<td>D5</td>
</tr>
<tr>
<td><strong>Dopamine</strong></td>
<td>0.9–2340</td>
<td>&lt;0.9–261</td>
</tr>
<tr>
<td><strong>Apomorphine</strong></td>
<td>0.7–680</td>
<td>122–163</td>
</tr>
<tr>
<td><strong>Effect on cAMP</strong></td>
<td>D1 and D5 increase cAMP</td>
<td>D2, D3, and D4 decrease cAMP</td>
</tr>
<tr>
<td><strong>Physiologic role</strong></td>
<td>Emesis</td>
<td>Erections</td>
</tr>
</tbody>
</table>

Kᵢ, binding affinity.

**Table 36.2 Melanocortin receptor localization and role**

<table>
<thead>
<tr>
<th>Localization</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>MC-1R Melanocytes</td>
<td>Skin pigmentation</td>
</tr>
<tr>
<td>MC-2R Adrenal cortex and adipose tissue</td>
<td>Steroidogenesis in response to ACTH</td>
</tr>
<tr>
<td>MC-3R Central nervous system and other tissues</td>
<td>Energy homeostasis</td>
</tr>
<tr>
<td>MC-4R Neural tissues Hypothalamus</td>
<td>Sexual function Obesity (MC-4R inactivation) Lean phenotype (MC-4R activation)</td>
</tr>
<tr>
<td>MC-5R Peripheral human tissues</td>
<td>Exocrine function Sebaceous gland function</td>
</tr>
</tbody>
</table>

MC, melanocortin; MCR, melanocortin receptor; ACTH, adrenocorticotropic hormone.
resulted in trial drop-out or use of anti-emetics. Nausea is dose-related and improves with continued dosing.\textsuperscript{33,35,36} In the forced-dose-escalation European clinical trial, 4.7\% and 1.6\% of the 507 patients taking apomorphine SL and placebo, respectively, dropped out of the trial as a direct result of drug-related adverse events.\textsuperscript{33} Data from a double-blind crossover comparison of apomorphine 3 mg and 4 mg documented an improved risk–benefit profile for the 3 mg dose base on a comparison of the incidence of nausea with a firm erection enough for intercourse. However, the tolerability profile of apomorphine SL is enhanced when dose optimization is followed.\textsuperscript{34}

**Cardiovascular safety**

Data from the first three crossover studies reported no deaths, myocardial infarction, cerebrovascular accidents, or priapisms. However, 4 of 690 patients (0.6\%) experienced brief (approximately 60 seconds) and self-limited syncopal episodes. Interestingly, 7 of the patients who suffered syncopal episodes continued to use the drug without further events. In addition, Holter studies demonstrated no arrhythmias.

Apomorphine in patients with underlying conditions (i.e., hypertension, CAD, diabetes, and benign prostatic hyperplasia) was well tolerated.\textsuperscript{35} In addition, the cardiovascular safety of the concomitant use of apomorphine 5mg with angiotensin converting enzyme inhibitors, beta-blockers, diuretics, calcium-channel blockers, alpha-1-blockers, and nitrates was investigated by Fagan et al. They reported minimal changes in blood pressure after repetitive orthostatic stress.\textsuperscript{38}

**Melanocortins in sexual function**

M-II\textsuperscript{34,39} and PT-141\textsuperscript{40–42} are synthetic melanocortin agonists, which have been shown to be effective in the management of ED in humans.

**Melanotan II**

**Efficacy**

A double-blind, placebo controlled crossover study with MT-II of 10 men with ED using real-time RigiScan monitoring reported that 8 of the 10 men developed clinically apparent erections after MT-II administration. Mean duration of tip rigidity (>80\%) was 38 minutes and 3 minutes for MT-II and placebo, respectively.\textsuperscript{38} In a subsequent study by Wessells et al., subcutaneous administration of MT-II to men with ED resulted in penile erections (mean rigidity score 6.9 out of 10) without sexual stimulation. MT-II and placebo mean duration of tip rigidity (>80\%) was 45.3 minutes and 1.9 minutes, respectively. In addition, the level of sexual desire was significantly higher with MT-II administration.\textsuperscript{39}

**Tolerability and safety**

Transient nausea, stretching and yawning, and decreased appetite were reported with MT-II administration.\textsuperscript{38} However, a subsequent study by the same investigators reported that four of 19 injections were associated with severe nausea.\textsuperscript{39}

**PT-141**

**Efficacy**

Molinoff et al. demonstrated that administration of PT-141 to healthy men and patients with ED resulted in a rapid and dose-dependent increase in penile responses.\textsuperscript{40} Subsequently, Diamond et al. showed in a double-blind, placebo-controlled study that intranasal administration of PT-141 to healthy males and to sildenafil-responsive ED patients resulted in statistically significant erections when compared with placebo.\textsuperscript{41} More recently, Rosen et al. investigated the effects of subcutaneous administration of PT-141 (0.3–10mg) to healthy males and to patients with ED who report an inadequate response to sildenafil. The investigators showed a statistically significant increase in erectile responses in healthy men at doses greater than 1.0mg in the absence of audio–visual–sexual stimulation. More importantly, patients with ED who reported inadequate responses to sildenafil experienced statistically significant penile erectile responses to subcutaneous administration of 4mg or 6mg of PT-141.\textsuperscript{42} Diamond et al. investigated the safety and efficacy of the co-administration of sub-therapeutic doses of intranasal PT-141 (7.5mg) and sildenafil (25mg) to 19 patients with ED who responded to sildenafil or vardenafil. Co-administration of PT-141 and sildenafil resulted in significantly greater erectile response (on RigiScan) than sildenafil alone.\textsuperscript{43}

**Pharmacokinetics**

Intranasal administration of intranasal PT-141 (4mg, 7mg, 10mg, and 20mg) resulted in peak plasma concentration values of 14.9ng/mL, 90.1ng/mL, and 140.5ng/mL with a median time to peak concentration of 30 minutes and a half-life of 1.85–2.09 hours.\textsuperscript{42}

**Tolerability and safety**

PT-141 was safe and well tolerated in all clinical trials.\textsuperscript{40–43} The most common adverse events were flushing and nausea. In addition, no significant changes in vital signs, laboratory tests, electrocardiography, or physical examination were reported.\textsuperscript{41}

**Novel central-acting drugs in the treatment of erectile dysfunction**

**Oxytocin**

When the oxytocin patent was revoked, the pharmaceutical industry lost interest in the potential role of oxytocin in the management of men with ED. However, early clinical investigations showed that oxytocin was effective in men with psychogenic ED.\textsuperscript{44–46} These observations were subsequently supported by preclinical studies showing that oxytocin injections to the PVN resulted in erectile responses in the rat model.\textsuperscript{47}
Glutamate
Rampin et al. showed that glutamate released after genital stimulation acts at AMPA and NMDA receptors. In addition Song et al. reported that hippocampal injection of glutamate receptor agonists resulted in erectile activity.

Hexarelin analogs
Intraventricular or systemic administration of hexarelin analogs induces penile erectile activity in the rat model. Melis et al. showed that two hexarelin analogs induced penile erections by increasing central oxytocin transmission at the level of the PVN.

5-Hydroxytryptamine-2, agonist
The observation that a metabolite of trazadone (mCPP) is a 5-hydroxytryptamine (5-HT)-2 receptor antagonist capable of inducing penile erections in the rat model, led to several clinical trials in the use of trazadone in the management of ED. However, poor efficacy has decreased the initial interest.

Summary
Scientific advances in the understanding of central nervous system signaling and regulation of penile physiology has allowed the development of the first central-acting ED drugs (apomorphine, MT-II, PT-141). Based on the available data, these drugs seem to be safe and effective in the management of men with ED. However, comparison trials between apomorphine and sildenafil have clearly favored the latter.

On the other hand, co-administration of central-acting drugs and PDE-5 inhibitors may result in better efficacy and tolerability. Development of more selective dopamine receptor agonists, melatonotonin agonists, or other novel central-acting drugs may result in better efficacy and decrease adverse events.

REFERENCES


Intracavernosal therapy for erectile dysfunction

Carsten Maik Naumann, Moritz Franz Hamann, Sascha Kaufmann, Amr Al-Najar, Christof van der Horst, and Klaus-Peter Jünemann

Introduction

The era of intracavernous drug administration had its onset in the early 1980s, now almost 30 years ago. It was on 11 January 1980 that Virag placed an injection of 80mg papaverine hydrochloride directly into the inferior epigastric artery, which was anastomosed to the cavernous body of the penis in the course of a Michel I Operation. According to his reports, this procedure bestowed a 3-hour episode of firm erection upon the 46-year-old patient.1 To support these incidental findings, Virag subsequently carried out comprehensive studies on the effects of vaso-dilatory drugs on the erectile tissue of the penis. Two years later, in 1982, the methodological option to achieve and maintain an erection by intracavernous application of vasoactive agents was made known to the medical public. The ability to initiate erections via local physiological mechanisms and without sexual stimuli shoked up the diagnostic procedures and treatment modalities of erectile dysfunction (ED) at that time, and set new standards.2

Recognizing the widespread therapeutic opportunities of this method, the following decade was devoted to directed clinical and basic research, investigating numerous pharmacological agents with respect to their suitability for intracavernous injection (ICI) therapy. In principle, all agents that promise smooth muscle relaxation, such as papaverine, alpha-adrenergic antagonists, prostaglandins, vasoactive intestinal polypeptide (VIP), calcitonin gene-related peptide, and nitric oxide (NO) donors (lisidomine, sodium nitroprusside) were submitted to pharmacological investigations. Since most of the active substances never reached the stage of official approval or were even accepted for off-label use, only three groups of drugs are currently in use for ICI: papaverine, alpha-adrenergic antagonists (phenolamine, moxisylyte) and prostaglandin-1 (PGE-1; alprostadil). Throughout these early studies, the enormous potential of auto-injection for home use in patients with ED became evident. While some investigators focused on single substances only, Zorgniotti and Lefleur reported the application of a mixture of papaverine and phentolamine, which was effective in 72% of patients treated.3 In contrast to the initial office-based injection treatment pursued by Virag and his colleagues, these patients were instructed in the technique of auto-injection.

In the same year, Hedlund and Andersson published their findings on the relaxation effect of prostaglandin on human penile tissue.4 But it was not until 1988 that Stackl et al. reported the effectiveness and safety of alprostadil in home self-injection therapy.5 In further studies by McMahon and Bennett and Barada,6 the use of a triple-drug combination of papaverine, phentolamine, and alprostadil was shown to be as effective as alprostadil alone, which consequently became the first drug approved in the USA by the Food and Drugs Administration for the treatment of ED.7 Since then, intracavernous injection of alprostadil has gained worldwide acceptance and became a first-line treatment option in ED. Combinations of papaverine, phentolamine, and alprostadil still remain treatment options in patients in whom monotherapy has failed or who suffer from significant side-effects.

Up to 1998, ICI therapy was the only effective, non-invasive treatment option in ED. But the introduction of phosphodiesterase (PDE) type 5 inhibitors to the field of ED treatment has challenged self-injection treatment as the first-line option. Today, it has generally been downgraded to a second-line option for the majority of ED patients. Nevertheless, ICI maintains its important role in diagnostic procedures and also in those patients where PDE-5 inhibitors are contraindi-cated or have turned out to be ineffective.

Pharmacology

There are three main peripherally acting drugs for intracavernous treatment of erectile dysfunction: PGE-1, papaverine, and phentolamine. PGE-1 was the first drug approved and the only drug approved worldwide for intracavernous administration.8,10 While widely used, combinations of papaverine and phentolamine have not received approval outside Europe for treatment of ED.6,11 These drugs have in common that they induce erection through an increase in corporal smooth muscle relaxation. Direct ICI leads to a high local concentration of acting agents and results in a favorable combination of local effects and systemic side-effects.

Prostaglandin E-1

PGE-1 acts via specific extracellular receptor binding, which in turn stimulates the intracellular enzyme adenylate cyclase.
This causes a rise in intracellular cAMP by conversion of ATP. The rise in intracellular cAMP results in smooth muscle relaxation via a fall in cytoplasmic calcium concentration.

**Phentolamine**
Phentolamine is a non-selective alpha-1- and alpha-2-adreno-receptor blocker. Erection is promoted by blockade of the tonic sympathetic neuronal activity and an increased supply of nitric oxide (NO) via a non-adrenergic, non-cholinergic effect on NO synthases (NOS).

**Dose finding**
The dose depends on the etiology of the ED, and it needs to be estimated initially. Severe vasculogenic ED requires higher initial doses, while administration of smaller doses promises therapeutic success in neurogenic and psychogenic ED.

**Technique of administration**
The drug is administered with a fine needle into the side of the shaft of the penis and gently massaged throughout the shaft for 30 seconds. Erection usually occurs within a period of 10–15 minutes.

**Efficacy**
The rationale for intracavernous treatment of ED is to gain good local efficacy with small doses, leading to fewer systemic side-effects. Monotherapeutic approaches as well as combination treatment options are available. In addition to an immediate therapeutic success, an increase in spontaneous erections as a result of improved penile circulation and oxygenation after long-term self-injection has been described.\(^{12,13}\)

**Monotherapy**
PGE-1 (general dosage 5–40μg) is the main representative of a single treatment approach. It is the most effective substance in monotherapy, with a reported efficacy rate of 70–75%.\(^{14}\) Phentolamine used alone is associated with a poor erectile response, as is the case for papaverine (with a reported success rate of 31%).\(^{15}\) The two substances are therefore mainly used in combination treatment.

**Combination treatment**
The basic aim of combination therapy is to combine the different modes of pharmacodynamic actions and thereby to reduce the dosage and accompanying side-effects of each individual drug. The 'Bimix' of papaverine (general dosage 7.5–45mg) plus phentolamine (general dosage 0.25–1.5mg) has been widely used and has shown a slightly lower success rate of 61–71% than PGE-1 alone.\(^{16}\) The 'Trimix' of papaverine (8–16mg), phentolamine (0.2–0.4mg) and PGE-1 (10–20μg) is associated with the highest available efficacy rate of 92%.\(^{17}\)

**Side-effects**
The most frequent side-effect of PGE-1 is penile pain after injection (13–80%), which occurs more frequently at doses above 15μg. Combination with sodium bicarbonate or procaine reduces these pain sensations. Prolonged erections (for more than about 4 hours after injection) are a rare event with PGE-1, with an estimated risk of 1%; this is due to a faster decrease in local concentration than occurs with papaverine.\(^{18}\) Cavernosal fibrosis occurs in 7.5–11.7% of patients using PGE-1, but usually heals up in 50%.\(^{17}\) Monotherapy with papaverine has been abandoned, owing to its hepatotoxic effects and a prolonged erection rate of up to 18%. The side-effects of phentolamine–papaverine in combination therapy resemble those found in papaverine monotherapy, with priapism in 15% and fibrosis in 12%.\(^{19}\)

**Indications and contraindications**
Today, ICI of vasoactive substances is considered to be a second-line treatment, although it has been proved to be highly effective in the treatment of ED. It can be used both in diagnostic and therapeutic approaches.

**Pharmacotesting**
ICI of vasoactive substances is a reliable procedure to differentiate between vasculogenic and non-vasculogenic ED. In general, a full erection after 10–15 minutes rules out severe arterial or venous insufficiency. In order to improve the response to ICI, the patient is allowed to stimulate himself if a full erection is not achieved or lasts only for a short time. Failure after ICI and stimulation is a good indicator for the presence of vasculogenic ED. Color Doppler imaging provides further information for distinguishing veno-occlusive dysfunction from arterial insufficiency. Patients with needle phobia or anxiety may not respond to this test.\(^{20}\)

**Indications**
Nowadays, PDE-5 inhibitors are first-choice agents in the therapy of ED. Basically, ICI is indicated if PDE-5 inhibitors fail, are not tolerated, or are contraindicated.

**Contraindications**
Common contraindications include allergies against any of the constituent drugs (alprostadil, phentolamine, or papaverine) and the presence of hematological conditions such as hypercoagulable states or sickle cell anemia, which can lead to prolonged erections.
Satisfaction

Men who seek professional help for treating their ED generally have a low level of satisfaction with their sex life and this in turn is highly predictive of their overall psychological status. Consequently, successful treatment enhances the level of satisfaction with their lives, particularly regarding the sexual quality of life.

The efficacy rate for the use of ICI in treating ED varies, owing to a number of factors, including the type of agent used and the age of the patient. Furthermore, the level of education is associated with the degree of acceptance for receiving such a mode of treatment. The efficacy can be reviewed with regard to different aspects, one of which is the degree of satisfaction of the patient and, not less importantly, the satisfaction of the sexual partner. The primary efficacy criterion, however, is the ability of the patient to achieve a rigid erection sufficient for vaginal penetration and performance of sexual intercourse. The degree of efficacy tends to increase the longer the period that the ICI has been applied. A rise in efficacy from almost 90% in the first year to almost 96% in the fourth year has been described.

ICI has met patients’ expectations in terms of efficacy, ease of use, tolerance, and improved sex life. All of this should encourage physicians and patients to use ICI when PDE-5 fails inhibitor therapy, is not well tolerated, or is contraindicated.

Age plays an important role in the satisfaction rate of the patient. Patients aged between 25 and 40 years tend to have a higher rate of dissatisfaction than those over 40 years. Table 37.1 shows satisfaction rates with different ICI therapies ranging between 80.3% and 91.4%, including patients with partial and full satisfaction. In addition, ICI is associated with substantial improvements in several aspects of quality of life; the largest improvement being in mental and social health, including anxiety, depression, and self-esteem.

All of these tend to be noted as early as 6 months after initiation of the treatment and tend to become even more notable in those receiving the treatment over a longer period of time.

Some of the factors responsible for dissatisfaction with or rejection of ICI are the inability to achieve adequate penile rigidity, the drugs being too expensive, the association with pain, needle phobia, the lack of spontaneity, return of spontaneous erection, the absence of a sexual partner, and alteration in the shape of the penis. Other factors can also relate to the sexual partner; the most common reason for partner dissatisfaction being the inability of the partner to achieve adequate penile rigidity. Among further reasons mentioned were the lack of sexual desire, the above-average duration of the erection, deterioration in the general health condition of the partner, and a complicated procedure. Close initial observation and monitoring of patients is very important in order to determine the degree of patient acceptance at an early stage, since the high drop-out rate is registered chiefly during the initial period of therapy. The level of acceptance tends to be higher in those who accept the treatment over a longer period of time. Furthermore, the degree of satisfaction of the sexual partner, together with the partner’s degree of willingness to help, plays an important role in the degree of acceptance. Once the treatment is accepted, adequate training and detailed medical follow-up are crucial.

Table 37.1 Satisfaction rates of different agents in ICI therapy

<table>
<thead>
<tr>
<th>Patient</th>
<th>Satisfaction</th>
<th>Age (median)</th>
<th>Number of</th>
<th>Agent</th>
<th>Instrument</th>
<th>Symptom score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virag et al. 1991</td>
<td>84.8%</td>
<td>Not mentioned</td>
<td>615</td>
<td>Papaverine, papaverine-phenolamine, ceritine</td>
<td>Not mentioned</td>
<td>IIEF</td>
</tr>
<tr>
<td>Giuliani et al. 1994</td>
<td>81%</td>
<td>24–72 (not mentioned)</td>
<td>144</td>
<td>Alprostadil</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Post et al. 1998</td>
<td>91.4%</td>
<td>22–70 (54)</td>
<td>162</td>
<td>Alprostadil–Alfadex</td>
<td>Not mentioned</td>
<td>Erection assessment score 0–3</td>
</tr>
<tr>
<td>Purvis et al. 1999</td>
<td>87.4%</td>
<td>23–93 (56)</td>
<td>766</td>
<td>PGE-1, Papaverine-phenolamine, ‘Trimix’</td>
<td>D-penn/BD-injectors/OM autoinjector</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Shabsigh et al. 2000</td>
<td>85.1%-89.6%</td>
<td>30–79 (not mentioned)</td>
<td>111</td>
<td>PGE-1</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Alexander et al. 2007</td>
<td>78.3%</td>
<td>21–86 (62.1)</td>
<td>596</td>
<td>PGE-1</td>
<td>Not mentioned</td>
<td>IIEF, EDITS, DAN-PSS</td>
</tr>
</tbody>
</table>

IIEF, International Index of Erectile Dysfunction; DAN-PSS, Danish Prostatic Symptom Score; EDITS, Erectile Dysfunction Inventory of Treatment Satisfaction; PG, prostaglandin; OM, Owen Mumford Ltd; BD, Becton Dickinson.

Non-responders to phosphodiesterase type 5 inhibitor therapy

The therapy of ED is a multi-modal concept with different kinds of options. A fundamental change was introduced with the development and approval of sildenafil. Sildenafil is the oral PDE-5 inhibitor with the longest clinical experience and
has proved highly popular since its introduction in 1998. Today, sildenafil, as well as vardenafil and tadalafil, is an effective first-line oral treatment for ED. Sildenafil shows a high efficacy–safety profile, with success rates for all etiologies of between 50% and 80%. Patients with severe organic ED have a bias towards oral therapy because of its non-invasive approach.

A strong preference for PDE-5 inhibitors has been demonstrated even if this therapy produces lower cumulative response rates of 75% than intracavernosal injection therapy. The high burden of ED is shown in the willingness to pay for the treatment. The Cologne Male Survey has demonstrated that oral treatment of ED is the preferred option. Approximately 40 million patients with ED worldwide have been treated successfully with the three available PDE-5 inhibitors (sildenafil, tadalafil, and vardenafil). To be considered ineffective, each drug has to be taken at least six to 10 times with a plateau for satisfaction at around the eighth dose.

In the text below the reasons for non-response are described for sildenafil, because the focus in the available literature is on this particular drug. For a long time it was maintained that there were no prognostic factors that might predict success or failure with sildenafil. Penile erection requires intact vascular structure, endothelium, smooth musculature, and nerves. The limitation of PDE-5 inhibitors lies in the fact that a minimum level of NO is necessary. If alterations are severe, they cannot be compensated for by PDE-5 inhibition. Studies have demonstrated that progression of endothelial dysfunction and diminished cavernosal smooth muscle content are organic factors that lead to end-organ dysfunction and treatment failure of PDE-5 inhibitors. Each patient was asked to take eight doses of sildenafil with a maximum allowed dose of 100mg before being considered a sildenafil non-responder. Androgen treatment in hypogonadic patients unresponsive to any PDE-5 inhibitor therapy seems to result in an improvement of erectile function. Administration of sildenafil with testosterone has resulted in significantly better improvement of erectile function and better arterial blood flow than sildenafil alone in patients with low testosterone levels. Additional pharmaceutical products that lead to activation of, or an increase in, cGMP, as well as alpha-adrenoceptor antagonists, have also been used to treat ED. A combination of sildenafil with PGE-1 has led to an improvement in 47–100%, following a failure of monotherapy. Myldo et al. were also able to demonstrate an improvement in erectile function in 68% of the study group with combined therapy, consisting of intracorporal injection of alprostadil and administration of an oral PDE-5 inhibitor in men with a suboptimal response to monotherapy. Moreover, Mazo et al. have shown that the results of ultrasonographic measurements of post-occlusive changes in the diameters of cavernosal arteries after vardenafil administration are significantly associated with the clinical efficacy of the drug in patients with arteriogenic ED. ICI may be capable of predicting the response to oral therapy. Most of the available data on the efficacy of sildenafil are based on questionnaires. By using cavernosometry and Doppler examination and by taking penile biopsies, Wespes et al. have shown that severe vascular lesions and atrophy of the cavernous smooth muscle are mainly observed in sildenafil non-responders.

Shabsigh et al. have shown that PGE-1 therapy can be used effectively and safely in men in whom initial therapy with sildenafil fails. It is also a good alternative for treatment of ED when PDE-5 inhibitors are contraindicated, especially for patients with severe cardiovascular disease. Moreover, some patients refractory to sildenafil have responded to ICI. Transurethral therapy with alprostadil (MUSE – medicated urethral system for erection) is an alternative non-oral therapy for ED. Before the development of PDE-5 inhibitors, a comparative study of MUSE and ICI showed alprostadil to be the ‘gold standard’ in the management of male impotence, owing to the superior efficacy and fewer side-effects of self-injection therapy. Hatzichristou et al. have evaluated the efficacy and preference of sildenafil or ICI in a group of impotent men currently using ICI. Sildenafil was found to be highly effective in 74.8% of ICI responders, although oral therapy was preferred by 61.2%.

If medical treatment fails, there are non-pharmaceutical options such as the vacuum constriction device and penile implants. Penile prosthesis implantation is considered a last resort, if all other therapies fail. New therapeutic strategies, such as anti-serotonergic substrates and growth hormones, offer promising new prospects for the therapy of ED but remain to be evaluated. In any case, therapy of ED should be performed in an individually suited way leading to a satisfying sexual life for every man affected by erectile dysfunction.

REFERENCES

Intracavernosal therapy for erectile dysfunction

Introduction

Invicorp is a combination of vasoactive intestinal polypeptide (VIP; aviptadil) and phentolamine mesylate for intracavernosal injection in the management of moderate-to-severe erectile dysfunction. VIP is a naturally occurring 28-amino acid neurotransmitter present in the male genital tract, and phentolamine mesylate is a competitive, non-selective alpha-1- and alpha-2-adrenoreceptor blocker. VIP has a potent effect on the veno-occlusive mechanism, but little effect on arterial inflow, whereas phentolamine increases arterial blood flow without showing any impact on the veno-occlusive mechanism. Studies using VIP in combination with phentolamine 1mg or 2mg led to the development of Invicorp. Clinical studies have shown that Invicorp is effective in ≥80% of men with erectile dysfunction (ED), including those who have failed to respond to other therapies, and it is associated with a very low incidence of penile pain and virtually negligible risk of priapism.

Invicorp may be used from an ampoule using a standard syringe, or via an autoinjector designed to reduce the usual anxieties of self-injection. Invicorp is approved and marketed in Denmark and New Zealand and is prescribed on a named-patient basis in the UK. We estimate that there are over 5.9 million men in the USA alone for whom oral ED drugs are not a viable treatment option and for whom Invicorp may offer a safe and effective alternative.

Rationale for clinical development

The regulation of penile erection is thought to be under neural control. The contraction and relaxation of the smooth muscle inside the tunica albuginea, which keeps the penis flaccid when contracted and allows it to erect when relaxed, is regulated by increased and decreased adrenergic tone, respectively. The concomitant release of neurotransmitters, including VIP, may also play a role in attainment and maintenance of the relaxed state. In the contracted state, only blood required for nutrition is circulating, whereas during sexual excitement the smooth muscle relaxes, arteries open, the cavernous muscles are stretched, and the cavernous space fills with blood.

Virag et al. demonstrated that the smooth muscle relaxant papaverine and the alpha-adrenoreceptor antagonist (alpha-blocker) phentolamine, given by intracavernosal injection, can be used to induce penile erection in the treatment of impotence. However, this and other studies found that phentolamine alone could not produce an erection. This is thought to be due to the fact that phentolamine produces a modest increase in arterial inflow, but has no effect on venous outflow. Sufficient arterial blood supply and a functional veno-occlusive mechanism are prerequisites for the attainment and maintenance of a functional erection (i.e. one allowing intromission).

Vasoactive intestinal polypeptide

Following the discovery of nerves possessing VIP immunoreactivity in the male genital tract, a putative role for VIP in local nervous control of the smooth muscle activity in the male urogenital tract was proposed. Shortly thereafter, Willis et al. suggested that VIP plays a role as a possible neurotransmitter involved in penile erection. VIPergic nerves are densely distributed in the penis, supplying the pudendal arteries and the cavernous smooth muscle cells, and VIP is released when erection is induced. When applied exogenously, VIP mimics the action of that released endogenously, displaying identical pharmacological characteristics.

The veno-occlusion resulting from the relaxation of smooth muscle appears to be under the control of VIP. In human corpus cavernous smooth muscle preparations, VIP has been found to act as a relaxant both in terms of spontaneous activity and for electrically pre-contracted tissue. These results are supported by the findings of Junemann et al., who showed that VIP has a potent effect on increasing venous outflow restriction. Ottesen et al. demonstrated that the concentration of VIP in cavernous blood increased up to 20-fold during penile tumescence and erection, which they attributed to local release of the peptide since they were unable to demonstrate a change in peripheral concentrations. VIPergic nerves were found to be depleted in the corpus cavernosum of impotent and diabetes-related impotent men. It therefore seemed likely that a deficiency in VIP might be responsible for ED, and this led to several investigations of VIP per se as an inducing agent for penile erection. A study was undertaken by Wagner and Gertenberg looking at the effect of VIP (1–20µg) in normal men. The study demonstrated that VIP alone will induce tumescence but not erection in normal males in doses of up to 20µg, suggesting that VIP could be the transmitter involved in relaxation of the trabecular smooth muscle and is involved to a lesser degree in the dilatation of the penile artery. The existence of a dual neurotransmitter system in the control of erection was postulated by these authors.
As an agent for the treatment of erectile dysfunction, the use of low doses of up to 1.2µg of VIP administered intracavernously was unsuccessful, and doses up to 60µg would not induce a useful erection, even with visual or tactile stimulation in more severely impaired patients. Severe facial flushing was also observed at doses of 60µg and it was concluded that the optimum dose for further investigation would be 30µg, which equates to 25µg of the formulation of Invicorp proposed for marketing, following adjustment in relation to water and acetate content.

The normal erectile process requires there to be both an adequate arterial inflow and an efficient veno-occlusive mechanism. VIP is therefore not an effective monotherapy for ED, but the rationale exists for combining VIP with a substance known to exert an affect on the arterial inflow.

Phentolamine mesylate
Phentolamine mesylate is a competitive non-selective alpha-1 and alpha-2-adrenoceptor blocker with a relatively short duration of action. Following intravenous injection its onset of action is rapid, the hypotensive response peaking within 5 minutes and lasting only 15–30 minutes. The ease with which endogenous catecholamines can displace phentolamine from the alpha-receptors accounts for the short duration of action.

Phentolamine causes vasodilatation and a fall in blood pressure as a result of two pharmacological actions; alpha-blockade and a direct action on vascular smooth muscle, suggestive of beta-receptor agonism. The principal alpha-adrenoceptor blocking properties of phentolamine are due to its antagonistic effects, with almost equal efficacy, at both the pre- (alpha-2) and postsynaptic (alpha-1) receptors. It is the latter that mediate smooth muscle relaxation.

In the dog model, intracavernous injection resulted in a 50–100% increase in arterial blood flow without showing any impact on the veno-occlusive mechanism, and in humans, the intracavernous injection of phentolamine 5mg resulted only in penile tumescence but not rigidity. Phentolamine is therefore not suitable as monotherapy.

Combining VIP and phentolamine
Invicorp was developed in Denmark by the inventors Fahrenkrug, Ottesen, and Gerstenberg, all of whom were clinicians active in the field of ED. It was initially evaluated clinically by Gerstenberg and Metz working in collaboration at two separate centers and developed further by Senetek PLC (California, USA).

A logical step in the search for an effective and safe treatment for ED was to combine VIP, which has a potent effect on the veno-occlusive mechanism but little effect on arterial inflow, with an agent that had the complimentary properties. Phentolamine was a good candidate in that:

- it is a licensed drug with a long history of use and an excellent safety record even at high intravenous doses;
- its off-label use in combination with papaverine was well documented for the treatment of ED, for which it was found to reduce the requirement for high doses of papaverine and reduce the adverse reactions associated with the latter; and
- it provided the missing pharmacodynamic property (compared with VIP alone) required for penile erection – namely its action on smooth muscle, increasing arterial inflow.

It is also now known that phentolamine when used as an intracavernosal agent in combination significantly prevents suppression of rigidity due to stress.

The first reported use of the combination of VIP with phentolamine was in 1989 though the authors used only either VIP 2µg or 4µg with phentolamine 2mg and found the combination to be ineffective. Phentolamine, in doses between 0.5mg and 3mg, had been established as an effective agent in combination with papaverine. The work using higher doses of VIP in combination with phentolamine 1mg on 2mg led to the development of Invicorp. This early long-term study included some dose ranging and demonstrated that phentolamine 0.5mg in combination with VIP was insufficiently efficacious for most patients with non-psychogenic ED, but that phentolamine 1.0mg appeared to give a generally more satisfactory response, with phentolamine 2.0mg being generally effective in those cases in which 1.0 mg was ineffective. The results of further (unpublished) dose-finding studies led to the conclusion that the combination of VIP and phentolamine is more effective than the individual components and that the higher dose combinations are more effective. This observation was confirmed by the subsequent clinical studies of Invicorp, in which the higher dose has been shown to be required by patients with more seriously impaired erectile function.

The dose–response observation was endorsed by an in vitro study that examined the response of stimulated excised human and rabbit corpus cavernosal smooth muscle to increasing doses of both VIP and phentolamine. VIP caused dose-dependent relaxation in both rabbit and human cavernosal tissue strips. Furthermore, alpha-adrenergic blockade with phentolamine potentiated this VIP-induced relaxation in a dose-dependent manner, demonstrating a synergistic effect between the two compounds in the relaxatory response. The in vitro study, together with the dose-ranging studies, endorse the benefits of combining VIP and phentolamine in the treatment of moderate-to-severe ED. The response to VIP per se was minimal at the doses selected for the combination therapy, and variable at higher doses. The response to phentolamine alone was minimal in all studies regardless of dose. Therefore, the combination of VIP and phentolamine for the treatment of non-psychogenic ED is based on valid therapeutic principles as required by the Committee for Proprietary Medicinal Products (CPMP) note for guidance on combination products. Each component has been shown to contribute to the effect, and the level of efficacy of the combination has been shown to be greater than that achievable by either of the components individually.

Current regulatory status
Invicorp is approved in Denmark, where it has been marketed by Ardana Bioscience (London, UK) since December 2006, and it has been prescribed on a named-patient basis in the UK.
since mid 1995. Regulatory filings are underway in other European countries to seek pan-European approval for Invicorp under the Mutual Recognition Process. Additionally, Invicorp has been approved in New Zealand, where it has been marketed by Douglas Pharmaceuticals (New Zealand) since June 2004. Safety concerns raised by the US Food and Drug Administration in 1999 in relation to carcinogenicity observed in animal models with a competitor’s phentolamine mesylate product resulted in a clinical hold being placed on Invicorp.\textsuperscript{27} The clinical hold has since been lifted following the outcome of a long-term rodent study of Invicorp; the initial carcinogenicity observed in animal models was deemed to have no relevance as an indicator of carcinogenic risk in humans. Invicorp has been licensed to Plethora Solutions plc (London, UK) for marketing within the USA, and this company is working towards marketing Invicorp in the USA by the end of 2009.

Clinical outcomes

Dosing

The initial prescribing dose is Invicorp 1 (VIP 25µg and phentolamine 1mg), which can be increased to Invicorp 2 (VIP 25µg and phentolamine 2mg) if the effect is insufficient. Invicorp is marketed either in ampoules or as a very user-friendly single-use pre-filled autoinjector device. In the autoinjector the needle is not visible before injection, therefore reducing patient anxiety. The pre-filled, single dose design also eliminates the need for reconstitution and so eliminates dosing errors. The needle is so small and the injection is so rapid that the injection is virtually painless. Injection of the medication does not commence until the correct needle depth has been reached, reducing the possibility of subcutaneous injection.

Erection-facilitating action: duration of erection and time of onset

Unlike other intracavernosal injections for ED, which result in full rigidity regardless of sexual stimulation, Invicorp is an erection-facilitating agent and intracavernosal injection results in tumescence or semi-rigidity, with most patients gaining full rigidity only following visual or tactile stimulation.\textsuperscript{3} This has resulted in reports from patients that the erection achieved with Invicorp is much more like the normal coital cycle than the action of papaverine or papaverine and phentolamine combination.\textsuperscript{5}

Injectable therapies for ED typically have a significant advantage over oral therapies in their rapid onset of action. The time from injection to onset of tumescence for Invicorp has been reported to be 0–5 minutes in 41% of patients and 5–10 minutes in 27% of patients.\textsuperscript{23} Reports of the duration of erection depend on the starting point of measurement and this has varied (i.e. from tumescence or full rigidity) but is typically within the range 30–240 minutes,\textsuperscript{2} although this may vary depending on the etiology of the ED.\textsuperscript{21} Unlike the action of papaverine (with or without phentolamine), which results in full rigidity until the action of the drug subsides (despite ejaculation), the rigid erection resulting from Invicorp injection and stimulation subsides to semi-rigidity or tumescence in a more natural manner after ejaculation, but with the potential for a new erection after further sexual stimulation.\textsuperscript{5}

Achievement of grade 3 erections

Several clinical studies have been conducted in Europe, and the published data from two large placebo-controlled phase 3 trials are summarized in Table 38.1.\textsuperscript{22,31} Both trials had identical entry criteria (1-year history of predominantly non-psychogenic ED based on medical history) and 84% of patients (in both trials) responded with a grade 3 erection to either Invicorp 1 or 2 during screening. This is similar to the 80% response reported by McMahon in a smaller pilot study;\textsuperscript{24} who also noted a complete response in patients with ED of neurogenic or psychogenic etiology, 78% response in patients with arteriogenic ED, and 33% response in patients with ED caused by venous leakage. It is worth noting that only patients failing to respond to Invicorp 1 in the screening or dose-titration phase were tested with Invicorp 2; hence, although the success

| Table 38.1  Efficacy of Invicorp in patients with a history of predominantly non-psychogenic ED |
|-----------------|-----------------|-----------------|-----------------|
|                | Screening phase | Placebo-controlled phase |                 |
|                | Grade 3 erections (n) | Patients (n) | Grade 3 erections per injection (n) | Active | Placebo | Active agent vs placebo comparisons |
| Sandhu et al. \textsuperscript{23} & Invicorp 1 & 204/304 (67%) | 188 | 1417/1886 (75%) | 45/373 (11%) | \textless 0.001 |
| & Invicorp 2* & 55/117 (47%) | 50 | 257/386 (67%) | 8/78 (10%) | \textless 0.001 |
| & Total & 255 (84%) | 238 | 1674/2272 (74%) | 53/451 (12%) | \textless 0.001 |
| Dinsmore et al. \textsuperscript{21} & Invicorp 1 & 155/234 (65%) | 91 | 655/877 (75%) | 21/179 (12%) | \textless 0.001 |
| & Invicorp 2* & 52/108 (48%) | 14 | 92/140 (66%) | 5/28 (18%) | \textless 0.001 |
| & Total & 197 (84%) | 105 | 747/1017 (74%) | 26/207 (13%) | \textless 0.001 |

Only patients failing to respond to a test dose of Invicorp 1 in the clinic and at home went on to receive the test dose of Invicorp 2 in the screening phase. Patients who did not respond to either dose of Invicorp in the screening phase did not proceed to the placebo-controlled phase. *4 and 6 subjects tested positive to Invicorp 1 but went on to test Invicorp 2 in error.
rate of Invicorp 2 at around 47% in both trials appears to be lower than with Invicorp 1 per se (around 65% in both trials) it represents success in a harder-to-treat group of patients. The overall success rate of Invicorp in achievement of grade 3 erection is therefore similar to published rates for other intracavernosal therapies.28

Importantly, treatment success is maintained when compared with placebo over a 6-month21 or 12-month29 period, with 74% of injections resulting in grade 3 erections (out of a total of 3285 injections in both trials combined), with no evidence of tachyphylaxis.

Invicorp also appears to be particularly successful in patients who have failed to respond to other intracavernous injections. A study designed to evaluate Invicorp in patients with ED resistant to other intracavernosal agents (including prostaglandin (PG)-E1 and papaverine–phentolamine) reported an overall response rate of 67% (n=47).20 This was further supported by results from a larger study where 73% (n=71) of patients who withdrew from previous therapies because of poor efficacy responded to Invicorp.23 Additionally, the lack of any reduced effect in older patients (aged over 60 years) in two trials suggests that this patient group, who may have more advanced organic impairment, are equally likely to benefit from Invicorp use.23,24 This finding is supported by the reports of patients receiving Invicorp on a compassionate use basis, with an 85% success rate in a group of 410 patients treated in the UK over a 10-year period22 and 179 patients treated in Denmark for up to 5 years.29 In the UK group, many patients had a high degree of comorbidity (28% had hypertension, 26% coronary heart disease, and 26% diabetes), 49 patients were over the age of 75 years, and 89% of prescriptions were for the higher dose; Invicorp 2.

Patient-reported outcomes

In two placebo-controlled trials, overall satisfaction with the drug and the autoinjector was assessed by the patients using a follow-up questionnaire.21,23 A similar questionnaire was also completed by patients and their partners on quality of life. Overall, ≥85% of patients were satisfied or very satisfied with the drug and ≥92% were satisfied or very satisfied with the autoinjector. In terms of improvements in quality of life, ≥81% of patients and ≥76% of their partners stated that their lives had been improved or greatly improved by the treatment.

Safety and adverse events

Not surprisingly, given the vasoactive properties of the components, facial flushing is the most commonly experienced adverse event following use of Invicorp and (following direct questioning) it is typically experienced after 33–50% of injections,21,23 with no significant difference between Invicorp 1 and Invicorp 2, but it is rarely stated as a reason for discontinuation of treatment. Other systemic side-effects are tachycardia or palpitations, headache, and dizziness, all being reported in ≤2.2% of injections.21,23 When Invicorp has been administered in the clinic, no changes were observed in blood pressure or pulse rate after the injections.21

Intracavernosal injection with PGE-1 produces painful erections in up to 30% of cases.21 More recent studies of modern formulations have found lower incidences, although a review of 20,000 patients over 15 years reported an overall incidence of 24%.31 In contrast, penile pain after injection with Invicorp is negligible. There was not a single report of pain following Invicorp injection (using autoinjectors) in one 6-month study including 236 men21 and with only 0.5% of injections in a 12-month study in which 2061 injections were used,23 despite ‘pain’ being one of the options available to tick in a list of possible side effects in both trials. In a 120-patient trial in which Invicorp was compared to PGE-1 (Caverject), Invicorp, both in ampoules and autoinjectors, produced erections without discomfort in over 75% of patients compared with only 37% using Caverject. Other local adverse effects reported following Invicorp use are bruising, bleeding at the injection site, and urethral bleeding, possibly related to injection technique, and all typically at an incidence of <8% of injections, which are similar to rates reported for placebo injections.20,21,23

It is well established that intracavernosal injection may cause cavernosal fibrosis, particularly in the case of papaverine. In a meta-analysis of the literature, including 15 retrospective studies, fibrotic changes were observed in 5.7% and 12.4% of patients after papaverine, and a mixture of papaverine and phentolamine, respectively.28 Fibrosis has not been reported with Invicorp, even following long-term use,22,28 and it also appears that there is no progression of pre-existing Peyronie’s plaques during or after Invicorp therapy.5

The incidence of priapism following intracavernosal therapy has been variously reported, possibly being influenced by the dosage used, the etiology of ED in the patient population reported, and the criteria adopted for the definition of priapism by different authors. Incidences for PGE-1 have varied between 0.07%32 and 1%,33 with papaverine and phentolamine combination (bimix) carrying a relatively high risk of priapism (lasting longer than 6 hours) of between 2% and >10%, depending on the dose used.28 The only reports of priapism in published trials using Invicorp are three occurring in 5044 injections in two large studies,21,23 equivalent to an incidence of 0.06%. There was not a single report of priapism occurring in patients who have been prescribed Invicorp on a compassionate-use basis in the UK for over 10 years.22 The risk of priapism occurring with Invicorp is therefore exceptionally low.

Conclusion

Invicorp is a highly safe and effective treatment for ED and, unlike many other ED therapies, it has no known contraindications. Invicorp has shown excellent results in a wide range of patients, in many of whom other therapies have failed, and it appears to be particularly suited to patients with moderate-to-severe ED. Other significant advantages include a rapid onset of erection after stimulation, typically within 2–5 minutes; natural termination of the erection after ejaculation; and a favorable safety profile. While phosphodiesterase type 5 inhibitors will undoubtedly remain the first-line treatment for ED, Invicorp offers an effective and safe alternative for the estimated 5.9 million men in the USA alone for whom oral ED drugs are not a viable treatment option.
REFERENCES


Vacuum systems for erectile dysfunction

Audrey C Rhee and Ronald W Lewis

Introduction

Continual media attention and the breakdown of sexual taboos have led to the population’s increasing awareness of their sexuality and, subsequently, to higher sexual expectations. Erectile dysfunction (ED) has burst forward not only into the medical field, but also into our vernacular. This is due to the increasingly vital aging population in conjunction with increases in the prevalence of certain chronic disorders (such as diabetes and peripheral vascular disease), and a decrease in the stigma attached to impotence.

The urologist’s arsenal for treatment of ED has exponentially increased in the past four decades. Options range from androgen therapy, phosphodiesterase (PDE) inhibitors, penile prostheses, vacuum erection devices, and injection or transurethral approaches. Therapy is individualized on the basis of the patient’s medical history, manual dexterity, expectation, social situation, and economic circumstances. In the modern age, two therapies have gained prominence as first-line therapy. They are PDE inhibitors and the vacuum erection system.1 The vacuum system (VS) offers patients a non-invasive, safe, and reliable option.

Historical perspective

In 1874, a physician, John King, described applying negative vacuum pressure to the penis for ED; however, once the glass cylinder was removed, the penis was unable to maintain an erection.2 In 1917, Dr Otto Lederer, from Vienna, Austria, issued a patent for his ‘surgical device’ to produce erections with a vacuum. The product was crude and difficult to use, and was not accepted by his medical peers.3

In 1960, Geddings D Osbon Sr became frustrated when told by his family physician that the only option he had regarding his impotence was abstinence.4 He devised a vacuum erection device from a standard bicycle pump, which he converted into a negative pressure pump for his personal use. Mr Osbon constructed a conduit to the mouth at the end of the device that produced the desired ‘mouth suction’. With this modification, he was able to market his Youth Equivalent Device®, which was initially sold as a marital aid and then as a medical device called ErecAid System® (Figure 39.1). Eventually, in October 1982 this device obtained approval by the Food and Drug Administration (FDA) for the treatment of ED in the USA. The first shipment of the ErecAid System® was in February 1984, with subsequent addition of the Chaney or Safe-T-ring. Table 39.1 details the current manufacturers who provide VS with a prescription or are covered by Medicare. In 1998, the FDA approved the over-the-counter sales of vacuum therapy devices in the USA.

While the VS was initially seen as a simple gadget, the medical community was eventually swayed. Drs Roy Withington and Perry Nadig pioneered its acceptance in publications of the first scientific papers regarding the VS’s efficacy and utility.5,6 The VS was considered a mainstream treatment option after Dr Tom Lue’s editorial in 1991 in the Journal of Urology, in which he stated that he recommended the vacuum erection device as first-line treatment to all his patients when not contraindicated.7

Mechanisms and principles

The vacuum erection device comprises three main components (Figure 39.2):

1. The cylinder
2. The pump
3. The tension or occlusion ring.

The cylinder is usually made of clear plastic. They are provided in different sizes to accommodate the variance in penile length and girth. Another option is to use an internal cylinder to modify the diameter. Larger cylinders are available by select companies for the patient who has significantly greater penile circumference than the cylinder will permit or for the patient who has severe angulation from Peyronie’s disease and therefore has difficulty removing the cylinder once the erection has been obtained. Some of the cylinder models taper out distally, with a nipple-like extension to attach plastic tubing to a handheld vacuum pump. Others have an open end at the distal aspect to permit direct attachment of the pump.

The pump design also varies. Some have a one-piece unit with a pump handle, while others have an outer pumping cylinder over an inner column. There is also a battery-operated pump, which was designed for patients who lack the manual dexterity or the strength to generate the hand-pumping motion. A majority of these pumps have a safety feature: a pop-off vacuum valve, which is activated after a
Shave the base of the penis for maximum results

Lubricate

Generously coat penis with water soluble lubricant such as K-Y jelly or a good face lotion. NO Vaseline. While cylinder is dry, double the rubber band in place around base of cylinder. – Now generously lubricate bands and base of cylinder. Lubricated bands will push off more easily.

Vacuum

After lubricating penis, place cylinder over penis and hold against body with light pressure. Place free end of flexible tubing in your mouth, and suck on tubing (like you would a thick milk shake) to remove air and to create a vacuum which pulls the blood down and engorges the penis with blood, thus producing the erection-like state.

Retaining band

Once the firmness you need is obtained, hold suction to maintain it, by placing tongue over end of tubing or use the clamp provided. Do not let the vacuum escape! When firmness is satisfactory then push rubber band off of base of cylinder onto base of penis. Release vacuum and remove cylinder.

Figure 39.1 Youth Equivalent Device, later renamed the ErecAid System®, required a mouth suction apparatus in order to develop sufficient negative pressure.

<table>
<thead>
<tr>
<th>Table 39.1 Current manufacturers in the USA that provide vacuum systems with a prescription or are covered by Medicare</th>
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<tr>
<td>Augusta Medical System – Augusta, GA</td>
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<td>Timm Medical Technologies – Eden Prairie, MN</td>
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<tr>
<td>Pos-T-Vac Therapy System – Dodge City, KS</td>
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certain negative pressure is produced (300–350 mmHg). Adequate rigidity is obtained after a vacuum pressure of 90 mmHg. Once sufficient engorgement of the penis has been reached and the tension rings have been placed around the base of the penis, the patient should then activate the release mechanism which releases the negative pressure.

Tension prosthesis rings come in a variety of schemes. Initially, Osbon manufactured elastic rings, which have since been replaced by soft-latex rings made by Timm Medical. These occlusion bands vary in size and tension (Figure 39.3a). Some rings are molded with a urethral-sparing notch along the

Figure 39.2 Three main components of the vacuum system: cylinder, ring, and pump. Image depicts Pos-T-Vac Therapy System.
Vacuum systems for erectile dysfunction

The inner curve of the ventral aspect of the ring (see Figure 39.3b). The notch helps to reduce ejaculatory obstruction while maintaining pressure on the corpora cavernosa. The tension rings should provide a tab or a string to facilitate its removal after use. There is also a tear-apart ring available from Augusta Medical System called the SureRelease (see Figure 39.3c).

The assembly of the apparatus can be performed by the patient or his partner. The proximal end of the cylinder, the penis, and the constriction band (or bands) need to be well lubricated with water-soluble jelly. The tension ring is then placed along the proximal aspect of the cylinder; some companies provide a loading cone to facilitate its placement (Figure 39.4). The cylinder is then placed firmly over the flaccid penis (Figure 39.5a). The pubic hair may need to be trimmed in order to obtain an adequate seal against the pubis. One hand should be around the cylinder to press the apparatus against the skin at the base of the penis. With the other hand, the patient can then begin to pump by hand or by activating the battery-powered model. Some devices allow the user to press the distal aspect of the cylinder against a table or a countertop to free one hand. Once adequate rigidity has been obtained, the pre-loaded tension rings are slipped off the proximal end of the cylinder and seated on the base of the penis (see Figure 39.5b). The vacuum is then released (by either a valve or a button) and the cylinder is removed from the penis (see Figure 39.5c). The patient is ready for intercourse. The occlusion bands are to be left in place no longer than 30 minutes. If the user would like to proceed with intercourse after 30 minutes, he must remove the ring, allow penile detumescence to occur, and repeat the process all over again.

The average time to obtain an erection is 2–2.5 minutes. The results vary with the pumping device. Of 100 patients, 88% obtained optimum tumescence and rigidity in 30 seconds to 2 minutes. Intermittent pumping may be necessary to obtain satisfactory rigidity to permit penetration (e.g. pumping for 1–2 minutes, releasing the pressure, and then resuming pumping for 3–4 minutes).

Vacuum erection is different from an erection obtained normally. Natural erections undergo a relaxation of the sinus smooth muscle within the corpora cavernosa, entrapping blood. Instead, with the VS, the negative pressure applied to the penis transmits passive engorgement of all the tissue compartments; in conjunction with the tension rings, the venous outflow is prevented. Bosshardt et al. confirmed these findings, reporting the presence not only of passive mixed congestion of arterial and venous blood, but also that a
large component of the increase in penile diameter was extrapenile tissue. Notably, for some patients, the erections (especially at the glans) obtained with the VS are larger than their natural erections.

Patient selection and contraindications

The VS has proven to be effective in treating ED in a variety of men. In an era in which oral therapy is considered first-line, men who are unable to take the medications or those who do not tolerate them can greatly benefit from the VS. Also, patients in whom other forms of treatment for ED have failed should be offered VS, either alone or in conjunction with other therapies. Furthermore, even though a patient does respond appropriately to oral, injectable, or transurethral treatments, he may not be able to afford the prescription. This patient population is often able to accommodate a one-time fee for the VS. Most importantly, the patient will need to be motivated. Those who have an understanding, well-established relationship are more likely to have long-term success with the device than others.

There are absolute and relative contraindications for the use of the VS. An absolute contraindication is if both the patient and his partner lack the manual dexterity to use the device. Also, patients with sickle cell disease should not be offered VS for their ED given the increased likelihood of developing priapism (i.e., sickle cell crisis).

The relative contraindications include anticoagulant uses, Peyronie’s disease, and tight foreskin. Patients who have

Figure 39.4 Loading cone provided by the Pos-T-Vac Therapy System.

Figure 39.5 Assembly and use of the vacuum system. (a) The penis is placed into the cylinder, which is pressed firmly against the pubis while the vacuum is applied. (b) After a satisfactory erection is obtained, the tension ring is slipped off the cylinder and seated onto the base of the penis and the cylinder may be removed. (c) The ring maintains the erection, but must be removed after 30 minutes.
capillary fragility should be adequately counseled that they are more prone to significant subcutaneous penile bleeding when using the VS. If a patient has severe angulation secondary to Peyronie’s disease, he may not be able to use the VS owing to the distortion of the penis when placed into the vacuum cylinder. Furthermore, men with tight foreskin may have discomfort if they do not obtain a circumcision prior to using the constriction device.

Results

There are various publications assessing both the patient and partner satisfaction with the VS. They have proven to be widely effective in the treatment of ED, even with the advent of PDE inhibitors.16 Erections satisfactory for penetration are obtained in approximately 90% of men.6,10,17-19 Likewise, the frequency of intercourse and orgasms increased, according to its users.20,21

Dr Perry Nadig reported long-term results of using the VS. The patients were separated into two groups: group 1 (short-term follow up of average of 1 month) and group 2 (long-term follow up of average of 29 months).21 Regular use was 69% in group 1 and 70% in group 2. The overall quality of the erection scored >90% regarding the rigidity of the erection, the length of the penis, and the circumference of the penis in both groups. Another clear indication of patient and partner satisfaction was if the men continued usage of the VS. Nadig found that regular use occurred in the majority of patients who had used the device successfully for at least 3 months; thus indicating that the drop-out rate is highest in the first 3 months.22 Long-term use by the patient may plateau to 50–69% after 2 years.5,23

In 1995, Dr Roy Witherington presented the largest and longest follow-up available on the external vacuum device.6 The Impotence Resource Center of the Geddings Osbon Foundation sent out a survey to its 34,777 registered owners of the Osbon products. Of the 7075 (20.3%) owners who responded, 5847 were considered valid, and 76% of the respondents remained continuous users, with 83.5% having sex as often as desired. Interestingly, after obtaining and using the VS, 65.4% reported improved self-image and 69.6% had an improvement in their relationship with their partner.

Spinal cord injury (SCI) patients have reported similar results as the general population, with improvement not only in the quality of their erections, but also in their sex lives and marital relationships.24 In a pool of 13 SCI patients, 92% were able to obtain an erection rigid enough for intercourse and all 13 men would recommend the VS to other SCI patients who suffered from erectile dysfunction.25 Of these 13 patients, two men developed sweating; none of the seven patients with T5 lesions or higher developed autonomic dysreflexia. Watanabe et al. reported findings consistent with other studies, in which 28 of 85 SCI patients elected to use VS as their first-line therapy.26 Particularly for this patient population with respect to decreased penile sensation, there is an increased risk of ischemic injury if the tension ring is left on for too long, and subcutaneous hemorrhage may develop if the patient uses anticoagulants and over-vigorous suctioning.25

Similarly, men with organic erectile dysfunction have satisfactory response rates with the VS. Adequate erections are obtained in:

- 70% of diabetic patients27-29
- 93% of patients with arterial insufficiency.30-32
- 70% of patients with venous leak20-32 and
- approximately 100% of patients after radical retropubic prostatectomy.23

One study suggested that, as the venous leakage became more severe, the VS was found to be more efficacious than other therapies.31 Among patients who have had their penile prosthesis explanted, 11 of 14 patients (3 men were reluctant to try the device) had satisfactory erections and successful intercourse with the VS.18 Ten of the 11 patients continued to use the vacuum system regularly.

Psychogenic erectile dysfunction was found to be effectively treated in combination with VS and psychotherapy. Wylie et al. described a trial separating two groups of patients with psychogenic ED, in which one group received both a VS and psychotherapy while the other group had psychotherapy alone.44 Improvement in erectile function was noted in both groups; however, a greater response was noted with combined therapy, 84% vs 60%. Segerreich et al. had similar findings, noting that 32% of the patients eventually achieved normal and spontaneous erections.12

Patients in whom single therapy has failed can greatly benefit from combination treatment. Ten men in whom individual therapy of either VS or injection had failed were treated with simultaneous injection and vacuum modalities.35 Penile strength, circumference, and buckling pressure were the end-points of the study. The study concluded that while the VS augmented the erectile response, combination therapy was found to be cumbersome by 2 of the 10 patients.

Raina et al. describe using sildenafil with VS in post-prostatectomy patients. A statistically significant improvement was found in both rigidity and satisfaction when comparing the VS versus the non-sildenafil in this set of patients.46 Moreover, 30% of the post-prostatectomy patients had a return of spontaneous erections 8 months after using combination therapy.

While it was clear that patients may achieve sufficient erections, it became apparent that overall patient and partner satisfaction (including effects on quality of life and marital relationship) with the VS needed to be evaluated. Turner et al. reported a drop-out rate of only 20% within a 12-month period.22 They found from their interviews that both men and their partners were pleased with improvements in erectile quality, increased partner arousal, increased frequency of orgasm, and sexual satisfaction. The VS was also associated with a decrease in general psychiatric symptomatology for men, increased male self-esteem, and increased marital satisfaction.19 The same group evaluating the partners of ED patients demonstrated that the women were equally pleased with either the injection therapy or the VS.97 The partners reported statistically significant increases in frequency of intercourse, sexual arousal, coital orgasm, and sexual satisfaction. Furthermore, they felt more at ease in their relationships and characterized sex as more leisurely, relaxed, and assured.
Side-effects and reasons for discontinuing use

In Dr Nadig’s long-term evaluation of both group 1 (n = 161) and group 2 (n = 115) (see above),3 men reported:

- pivoting of base of penis (35% in group 1, 29% in group 2)
- bruising of the penis (32%, 32%)
- penile petechiae (32%, 38%)
- pain or swelling after device use (16%, 28%)
- pain with orgasm related to the tension device (19%, 19%)
- occasional numbness (48%, 49%)
- increased climax or orgasm (38%, 50%)
- decreased climax or orgasm (23%, 23%).

Individual patients reported that the first five effects listed above occurred the majority of the time that the device was used; however, it was considered a major issue by fewer than 6% of the patients. Notably, Nadig has stated that the most frequent complaint of patients is the unnatural interruption of intercourse. Partners also reported the lack of spontaneity and hesitation about initiating sex as a negative aspect of using the VS.37

In some cases, partners were not pleased with how the penis becomes slightly cold to touch and becomes bluish in color due to cyanosis.4 Once the occlusion bands are placed, the drop in penile blood flow results in a decrease in penile skin temperature of about 1°C.41

There are case reports of more serious side-effects of using the VS. Skin necrosis and Peyronie’s disease have resulted from misuse of the device.38-41 To date, there has been no direct evidence that proves that the VS causes Peyronie’s disease. Fournier’s gangrene, urethral bleeding, and herniation of the scrotal tunica vaginalis have been also been reported as rare complications.

Many patients discontinued use of the VS for reasons unrelated to side-effects. Men reported not using the VS because of changes in their relationships – for example, divorce or death of a partner or loss of libido.42 Another 11% of men, after using the VS, reported the spontaneous return of their erections.3

Expanded applications

While there is a theory that the VS may cause Peyronie’s disease, there is some thought of using the device to aid in treating penile curvature.40,42 Dr Lue describes a small set of patients who had severe Peyronie’s disease with penile shortening. These patients underwent a circular venous graft to treat the curvature. Postoperatively, they were instructed to use the VS daily for 1 month after surgery for what the authors termed chronic intermittent stretching of the penis. The study suggested that using the VS helped patients to regain penile length after grafting.

Another possible application of the VS is penile rehabilitation after prostatectomy.43 Patients were divided into two groups: group 1 used the VS an average of 3.9 weeks after surgery at time of follow-up (9 months), and group 2 was observed without any erectile aids. Spontaneous erections returned for a similar fraction of patients in both groups; however a slightly greater number of these patients (17% vs 11%) had erections rigid enough for penetration. These results suggested a possible benefit in early intervention for post-prostatectomy patients. This topic continues to be debated, and more studies will need to be performed.44,45

Summary

ED has become a popular focus and topic between patients and urologists. With this in mind, it is vital to have available both invasive and non-invasive options for this patient population. The vacuum system offers a safe therapy that has minor or rare complications and is likely to remain a significant and successful treatment option.

REFERENCES

Integrated sex therapy: a psychosocial–cultural perspective integrating behavioral, cognitive, and medical approaches

Michael A Perelman

Introduction

After a decade-long dialogue between sex therapists and other sexual medicine specialists the old idea of a biopsychosocial model is being re-adopted as conventional wisdom. The etiology of erectile dysfunction (ED) is thought to be due to a dynamic combination of organic and psychosocial–cultural factors (PSCFs). Yet, the relative contributions of these factors continue to be debated. Fortunately, few still cling to 20th-century concepts, which reported that either of these factors typically accounted for 90% of the ED etiology.1,2

This chapter is rooted in one sex therapist’s perspective regarding the etiology, diagnosis, and treatment of ED. It summarizes clinicians’ adaptations of biopsychosocial models to optimize ED treatment for men and their partners. These approaches were types of combination treatment, which itself has a distinguished history in medicine. An ED chapter’s audience would typically be urologists and primary care physicians (PCPs). However, this chapter’s concepts are applicable to all sexual dysfunctions (SD), expanding the intended readership to a wider range of clinicians.

Etiology

Both organic and PSCFs play a role in the etiology of sexual function and SD, and consequently in the diagnosis and treatment of ED.3–6 Omnipresent psychogenic components exist in most potency problems. Anxiety may even exacerbate a mild organic situation into total deficit. The manifest deficit frequently exceeds the actual organic impairment even in ‘organically impotent’ men. Despite the degree of organic component, ED always has a psychogenic component – even if the ED was initially caused by illness, surgery, or other treatment.7

The importance of failure

Immediately subsequent to sildenafil’s 1998 launch, mental health professionals and others presented at meetings and published about the PSCF balance in the sexual medicine equation.1,5,8–11 Retrospectively, it seems intrinsically obvious that if etiology is multifaceted, treatments must incorporate that knowledge! Yet that viewpoint was not initially the consensus within the sexual medicine community. Now there is widespread recognition that simply restoring erectile function is often insufficient in helping patients or, especially, couples to resume a satisfying sex life.8–10 However, it was the examination of failure, and specifically non-responder discontinuation rates, that helped to raise greater recognition of the multifaceted etiology of ED.9,11–13

Following sildenafil’s launch, close to 90% of men who sought medical assistance for ED were treated with phosphodiesterase (PDE) type 5 inhibitors alone, with little additional counseling at all. Approximately 70% of these men reported improvement in quality of life13 yet discontinuation rates appeared to approach 50%.16,17 Some men tried PDE-5 inhibitors out of curiosity and never intended long-term use. Others discontinued ED treatments as a result of a lack of efficacy, a fear of side effects, cost, and overall poor health. Yet, there is no question that PSCFs were also major considerations. Both patient and partner PSCFs included mental status (e.g. depression), loss of confidence, fear of failure, unrealistic expectations, and performance anxiety. All of these affected treatment outcome. In addition, unconventional sexual arousal patterns (e.g. homosexuality, sadomasochism) sabotaged treatment. Over time, there were reality-based alterations in a partner’s sexual desirability that also affected both arousal and orgasmic response. Perhaps the most important PSCFs interfering with reversing ED and establishing a satisfying sex life were relationship issues.18 While partner pressure was a primary driver for seeking treatment, relationship issues were frequent causes of treatment discontinuation and failure.19–21

Shifting sexual health care delivery patterns

Furthermore, this discontinuation phenomenon occurred concurrent with shifting patterns in the health care delivery. PCPs became the principal providers for men complaining of ED. Rarely were sex therapists the first to see these men, as medicalization hit its apex by the end of the 20th century.1
Unfortunately, the sexual history obtained by these PCPs during their brief office visits was usually end-organ-focused. Significant PSCFs to restoration of sexual health were frequently unexamined. These PSCFs represented a significant cause of non-response and treatment discontinuation.22 For treatment to be optimized, the complexity of these obstacles should be understood.49,23 These barriers to success could be managed as part of the treatment, yet too few clinicians felt they had the necessary training or time.3,9 How might this complex etiology be conceptualized?

The Sexual Tipping Point®

One depiction of the role that both biogenic and PSCFs play in the etiology of sexual function and SD is The Sexual Tipping Point® (STP). This etiologic model provides a foundation for a fuller understanding of the interface between PSCFs and the medical and surgical treatments of ED (Figure 40.1).22 The mind and body both inhibit and excite sexual response.24 PSCFs may simultaneously excite (turn on) or simultaneously inhibit (turn off) sexual response. Reciprocally, organic factors, also, both excite (turn on) and inhibit (turn off) sexual response. These factors combine dynamically in a manner that predetermines a person’s sexual readiness or capacity. The point at which the person’s ‘turn-ons’ are meaningfully greater than their ‘turn-offs’ is their STP. Therefore, sexual response may be inhibited or facilitated as a result of a mixture of both PSCFs and organic factors. The STP is the characteristic threshold for the expression of a sexual response for any individual person, which may fluctuate dynamically within and between individuals for any given sexual experience.22 That threshold is determined by multiple factors for a given moment or circumstance, with one factor (or more than one) dominating, while others recede in importance.

The double-arrow signs (↔) adjacent to the ‘psychosocial-cultural’ and ‘physiologic and organic’ factors in Figure 40.1 represent the variable valences (weighting) of these component etiologic contributors. The physical factors that both inhibit (−) and excite (+) include, but are not limited to: anatomical, endocrinological, and neurological factors. For instance, these neurological factors can be both activated and deactivated, actively turning on or turning off like millions of microswitching stations. The ‘mental’ factors include various turn-ons (+) and turn-offs (−) in the realms of psychology (cognition, emotions, behavior), social interactions (relationships), and culture (contextual zeitgeist). These forces interact with each other in a unique way that influences the nature and quality of sexual capacity and experience at any moment. The balance beam symbolizes the dynamic or continuously readjusting nature of the STP. ED is a negative balance of these various complementary and opposing forces (‘turn off’), reflecting the fact that positive arousal (+) factors were not sufficient, or were overwhelmed by the negative (−) factors, mitigating erection.

Treatment

Besides raising consciousness regarding the multifaceted nature of the etiology of ED, examination of non-responder and discontinuation data increased research on treatment optimization. Initially, urologists improved efficacy and ‘salvaged failures’ by revised dosing instructions to include diet and timing, as well as dose repetition and escalation strategies.12,13 Optimization efforts were continually refined;

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Figure 40.1 The Sexual Tipping Point®: The characteristic threshold for the expression of a sexual response for any person, that may vary within and between sexual experience. ©2006 Michael A Perelman, from reference 3.
Brock et al. recently published results of a first-visit treatment optimization program, which incorporated a tear-off sheet, a brochure, and a video used to standardize and optimize dosing instructions for sildenafil-naïve men seeking ED treatment.\(^2\)

While these approaches resulted in some improvement, it was soon recognized by sex therapists that treatment optimization required a more sophisticated combination treatment that incorporated attention to PSCFs. In fact, it was postulated that combining sexual pharmaceuticals and sex therapy optimized treatment and required less medication, thus improving risk–benefit ratios.\(^9\)

**Combination treatment**

Combination treatment was not new, and sexual medicine was not the first specialty to use this approach. In many medical specialties, including urology, combination treatment referred only to a multi-drug regimen.\(^9\) Yet psychiatry had demonstrated the benefit of combining both psychological and pharmaceutical treatments for many conditions.\(^27\)–\(^29\) Sexual medicine had its own history of combination treatment. Sex therapists in the 1990s worked adjunctively with urologists, combining intracavernosal injection, intraurethral insertion, and vacuum tumescent therapy.\(^1,3,9\) Case reports and consensus panels summarized the evidence and strengthened the argument for combination treatment for ED.\(^5,9,11,17,23,31–34\) Both Althof and Perelman expanded upon these strategies and recommended a combination treatment approach for office practices to optimize treatment outcome and satisfaction.\(^4,14\) Their synergistic conclusions were supported by limited empirical evidence, yet their recommendations continue gaining adherents.

Who, what, when, where, and how?

Two alternative models for combination treatment were gradually adopted. First, primarily PCPs, but also urologists, added some sex education and counseling to their therapeutic armamentarium. ‘Sex counseling’ in this situation made use of techniques to overcome PSCF obstacles to patients’ sexual function and satisfaction.\(^9\) Physicians did this work themselves or used various physician extenders within their offices.\(^1,4,22\) In the second model, physicians collaborated with non-physician sex therapists, resolving ED through a co-ordinated multidisciplinary team approach to treatment.\(^2,23,33\) This author respectfully acknowledges his many outstanding physician sex therapist colleagues, but has used this language because the majority of sex therapists are non-physicians. Treatment format varied according to the preference and expertise of those healthcare providers. Additionally, it was influenced by the PSCF severity of the ED and by patient preference.

These models of combination treatment\(^1,4,7,23\) all suggested guidelines for managing ED that expanded, but continued to match, the type of treatment algorithm described in the ‘process of care’ model and other step-change approaches.\(^36,37\) Later, Perelman advocated a model of combination treatment for all SD.\(^4,23,36–41\)

Perelman recommended that clinical expertise, as well as the PSCF’s complexity, determine whether the treating physician worked alone (including the use of office physician extenders) or as part of a multidisciplinary team. Besides assessing all needed physical findings (by examination, laboratory testing, and so on) the physician diagnosed the patient as suffering from mild, moderate, or severe obstacles to successful restoration of sexual function and satisfaction. The physician attempted to identify the PSCFs (cognitive, behavioral, relational, and contextual–cultural) that were predisposing, precipitating, and maintaining the ED. The diagnosis was dynamic and continuously re-evaluated as treatment progressed. The clinician continued treatment or made referrals based on progress obtained. Perelman categorized these PSCF’s obstacles as follows:\(^4\)

- Mild – no significant or mild obstacles to successful medical treatment
- Moderate – some significant obstacles to successful medical treatment
- Severe – substantial or overwhelming obstacles to successful medical treatment.

While no objective data determined the criteria for diagnosing these three categories, they provided useful guidance. For instance, ‘severe’ usually required psychotherapeutic and/or psychopharmacologic intervention prior to the initiation of sexual pharmaceutical treatment. The treatment matrix in Table 40.1 suggested whether physicians treated by themselves or sought collaborative assistance.

Clearly a multidisciplinary team, including a sex therapist and multiple medical specialists, could treat almost every case, although severe cases usually require a greater number of office visits, with lower success rates, than moderate or mild cases. However, such a team was labor-intensive and frequently economically and geographically unrealistic. Yet, mild and/or moderate cases reflected common scenarios for which a solo physician could successfully treat by combining sex counseling with sexual pharmaceuticals. Physician difficulty with either moderate or severe PSCFs would lead to referral and presumably the use of the multidisciplinary team model.

**Sex counseling tips for physicians**

PCPs adapted the STP model within a combination treatment model, in which pharmacotherapy and brief sex coaching were combined into a more satisfactory, efficacious treatment.\(^4\) ‘Sex coaching for physicians’ provided a comprehensive discussion for non-psychiatrist physicians on incorporating counseling into their office practice to enhance ED.

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<tr>
<th>Table 40.1</th>
<th>Psychosocial–cultural factor (PSCF) severity determines ED treatment management format</th>
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<td>Physician sex coach</td>
<td>Rarely</td>
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<td>Multidisciplinary team</td>
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Adapted with permission from reference 4.
treatment efficacy and satisfaction. The article highlighted the following key areas of combination treatment:

- a focused sex history (sex status);
- partner issues;
- sexual scripts and pharmaceutical choice;
- follow-up and therapeutic probing to manage non-compliance, weaning, and discontinuation;
- relapse prevention; and
- referral.

Focused sex history
A focused history integrates psychosexual and medical factors in a flexible manner and can be adapted by a PCP with only 7 minutes’ consultation time available, or by a sex therapist with 45 minutes for a patient. Treatment for ED should be started as soon as possible, with re-evaluations based on patient response. The successful treatment of ED requires a specific dataset that provides answers to three key questions regarding diagnosis, etiology, and treatment:

1. Does the patient really have ED and what is the differential diagnosis?
2. What are the underlying organic and/or PSCFs?
   - What are the organic factors?
   - What are the maintaining PSCFs (e.g., current cognitions, emotions, behaviors)?
   - Are potential ‘deeper’ PSCFs present (e.g., incest, sexual orientation confusion, addiction)?
3. Are the PSCFs severe enough to require pre-treatment, or can these factors be bypassed or treated concurrently?

Sex status examination
The sex status is the single most important diagnostic tool at the clinician’s disposal and is consistent with the ‘review of systems’ common to all aspects of medicine. The sex status is a summation of the patient’s current sexual desire, arousal, and orgasmic capacity. The details of the physical and emotional circumstances surrounding the onset of difficulty are important for the assessment of both physical factors and PSCFs. It is informative to assess if the ED was slowly progressing with age, rather than an acute shift. Ascertain why the patient is seeking assistance at that moment in time. ‘Tell me about your last sexual experience.’ This request evokes descriptions of insufficient stimulation, lack of desire or arousal, fatigue, and negative thinking. When does anti-sexual thinking emerge? Is the patient anxious about sexual failure early in the day before sex is even on the horizon? Is he concerned about his partner’s thoughts or is he judging himself negatively? The mind is capable of derailing normal sexual arousal as well as interfering with the restorative benefit of sexual pharmaceuticals. To function sexually, men need sexy thoughts, not only adequate friction. Assess if the last sexual attempt was a typical experience. What were the differences between this experience and earlier ones. Comparisons that will inform the clinician of numerous etiological issues, including masturbation frequency and technique. Depending on the particular patient, the discussion of last sexual experience and an elaboration on current functioning will inevitably evoke information about previous approaches the patient attempted. The effects of such treatments should be assessed. Enquiries can be made about desire, fantasy, frequency of sex, and effects of drugs and alcohol.

The clinician should briefly screen for obvious psycho-pathology that would preclude initiation of ED treatment. There is a statistically significant increase in depression for individuals with ED, and the severity should be clarified. All patients with major depression should be queried for suicide risk. Treatment of ED may improve mild depression, while depressive symptoms might alter the effect of therapy of ED. A clinician’s history-taking must parse out whether the ED is causing depression or whether the depression and its treatment is causing the ED.

Partner issues
The sex status frequently leads to a brief review of the current relationship, which should be assessed for contextual factors and interpersonal relationship difficulties and for whether the partner has female sexual dysfunction. In reality most physicians lack the time for a thorough evaluation of all relationship issues even if the partner joins the patient for the office visit, which itself is not typically the case. Sensitivity to partner issues on the part of the physician is critical. However, despite the exhortations always to interview the partner when treating men with ED, it is partner co-operation and participation that are the key variables – not necessarily partner attendance at the office visits.

Spending an extra few minutes with the patient during the evaluation visit and recognizing the importance of follow-up and referral solves this potential conundrum.

Ask the man questions about himself, but also about his partner and their relationship. Evaluation of his sexual function must also capture information about her sexual function, attitudes, and behavior. What is her emotional readiness for treatment? When and how should treatment be introduced? The average man with ED waits 2–3 years before seeking assistance. By then, a new sexual equilibrium has been established within the relationship that may be resistant to change. What is her desire for sex? What are her concerns regarding his safety? What are her belief systems regarding the treatment processes that enable coitus? Her compliance may be affected by her perception of the treatment being artificial or mechanical: ‘Is it the sildenafil, or me?’ What is her health status (vaginal atrophy for example) and physical readiness for sex, her capacity for lubrication, and her need for stimulation? We know that the prevalence of ED increases with age. We know that older men tend to have older, postmenopausal partners. Female sexual dysfunction is often detected in the partners of men with ED, including urogenital atrophy, dyspareunia, lack of desire, and vaginismus, which may interfere with resumption of intercourse even once his sexual capacity is restored.

Assess whether sexual relations were ever good with the current partner, what changed, and what is the patient’s view of causation. Whether or not the problem is partner-specific, the
clinician must ascertain which of several categories are relevant: inadequate sexual technique, poor communication, incompatible sexual script, or no physical attraction. Screen for severe difficulties in the couple’s relationship through inquiry. A reassuring, ‘No one’s relationship is perfect; what do you two argue about?’ can be helpful. Additionally, monitor the degree of acrimony when the patient describes his complaints. For example, is the anger, hurt, or sadness a causative factor, or are they mild emotional frustrations of daily life?

Fortunately, many partners of both men and women are co-operative, which partially accounts for the high success rates of medical and surgical interventions. Indeed, most of the co-operation goes unexplored. The co-operation is assumed, based on post hoc knowledge of success. In other words, serendipitous matching of sexual pharmaceutical and previous sexual script equaled success: ‘we did what we used to do, and it worked’. Many of these partners are never seen by the treating physician, nor is their attendance necessary for success.

Sexual scripts
Understanding the couple’s ‘sexual script’ can help the clinician to fine-tune pharmaceutical selection, leading to better orgasm and sexual satisfaction, not merely improved erection. This transcends, ‘try it, you’ll like it’. Knowledge of pharmacokinetics (onset, duration of action, and so on) plus sexual script analysis helps to optimize treatment. Sexual script in this situation refers to style and process of the couple’s pre-morbid sex life. Instructions should focus on returning to previously successful sexual scripts – as if medication was not a necessary part of the process. Fitting the right medication based on pharmacokinetics to the couple will increase efficacy, satisfaction, and compliance, and will improve continuation rates. Rather than changing the couples’ sexual style to fit the treatment, try to fit the right medication to the couple.

Follow-up and therapeutic probe
Healthcare professionals can increase their success by scheduling follow-up on the day they prescribe. As with any therapy, follow-up is essential to ensure an optimal outcome. Initial failures examined at follow-up reveal critical information. The pharmaceutical acts as a therapeutic probe, illuminating the causes of failure or non-response. Retaking a quick sex status provides a convenient model for managing follow-up. Other components of the follow-up visit include monitoring side-effects, assessing success, and considering whether an alteration in dose or treatment is needed. A continuing dialogue with patients is critical to facilitate success, prevent relapse, and differentiate treatment non-responders from biochemical failures.

Partner co-operation must be anticipated before treatment, and follow-up provides an opportunity to confirm whether or not such co-operation is present. If co-operation is not present, the recognition of a need for contact with the partner should increase. If the partner’s support for successful resolution of the ED is not present, then active steps must be taken to evoke it. Sometimes a referral for adjunctive treatment to a sex therapist may be required.

Weaning and relapse prevention
Generally, the concept of relapse prevention has not been incorporated into sexual medicine. Yet ED’s progressive pathology may play a role in altering the threshold for response and in a potential re-emergence of dysfunction. Additional follow-up sessions help the patient to stay the course and provide an opportunity for additional treatment. These concepts are derivative of an addiction treatment model in which intermittent but continuous care is the treatment of choice. Additionally, sex therapy concepts offer potential for minimizing dose and temporarily or permanently weaning the medication based on severity of PSCFs and organic risk factors. Over time, the progressive exacerbation of either organic factors (such as endothelial disease) or PSCFs may have an adverse impact on a previously successful treatment regimen. Most physicians’ initial response was to escalate dose and provide alternative medications. However, these processes may be modulated by sexual counseling, provided by the physician or through referral.

Referral, consultation, collaboration?
The physician’s time crunch is manageable, if counseling of the ED patient is brief. With more severe PSCFs the modal choice was a simultaneous initiation of ED treatment along with a referral to a mental health professional. The more severe the PSCFs, the less likely that patient–partner education will successfully augment treatment, in and of itself. Inevitably, a referral would be required, albeit not necessarily accepted.

Working together: a multidisciplinary team approach
Having a multidimensional understanding of ED does not mandate a multidisciplinary approach. A solo practitioner may question whether to collaborate within a multidisciplinary team or whether to provide combination treatment by himself or herself. How does one decide? If one is not inclined to counsel or is uncomfortable, consider working conjointly with a sex therapist. All clinicians should be encouraged to practice to their own comfort level. Indeed, some PCPs will not have the expertise to diagnose PSCFs adequately, quite apart from their ability or willingness to treat these factors. Awareness of their own limitations will appropriately prompt these physicians to refer their patients for adjunctive consultation.

In-house multidisciplinary team
The concept of an in-house multidisciplinary team is a simple one: sometimes two heads are better than one. Treatment may require a multidisciplinary team in cases of severe dysfunction, and such dysfunction may be recalcitrant to success even in
this ideal circumstance. There are many models for working together. Team approaches and composition will vary according to clinician specialty training, interest, and geographic resources. Some physicians work alone, or have set up in-house multidisciplinary teams in which nurses, physician associates, and master’s level mental health professionals provide the sex counseling. This approach has obvious advantages and disadvantages.

Research evidence supporting a multidisciplinary combination treatment approach is increasing in the areas of treatment optimization, adherence, and continuation. Recently, ED patients who received sildenafil and a structured education or counseling group treatment achieved higher rates of clinical success within the first 4 weeks of therapy than a sildenafil-alone cohort. However, that study was limited to men with ‘psychogenic’ ED. For men with ‘psychogenic’ ED, meta-analysis has shown that men randomized to receive group therapy plus sildenafil showed significant improvement of successful intercourse and were less likely than those receiving sildenafil only to drop out. Yet, it is hypothesized here, that men with more moderate and severe ED of mixed etiology will benefit the most from combination treatment, which will increase continuation and optimize outcome.

Virtual multidisciplinary team

In cases of more severe PSCFs, patients will be ‘referred out’ for psychopharmacology, cognitive–behavioral therapy, and marital therapy in various permutations, provided by doctoral level mental health professionals. However, typically clinicians refer within their own academic institution or within their own professional referral network – a kind of ‘virtual’ multidisciplinary team. Endocrine, gynecologic, or urologic referrals for the patient or partner may also be required.

Whether the referral is physician or patient initiated, sex therapists are ready to effectively assist in educating the patient about maximizing response. They re-motivate people in whom initial medical treatments have failed, as well as help patients to adjust to ‘second- and third-line’ interventions. They help to make patients receptive to trying again. Sex therapists are equipped to resolve the intrapsychic and interpersonal blocks (resistance) to restoring sexual health. They are trained to manage the most difficult cases involving process-based trauma, which may be replicated in the current relationship. Sex therapists working adjunctively with a PCP or urologist could provide all the sex counseling discussed above, as well as managing PSCFs with greater therapeutic depth. Sex therapists can enhance hope, facilitate optimism, and maximize placebo response. There can be an increased individualization of treatment format, by fine-tuning therapeutic suggestions, as well as improving response to medication. Sex therapists have a sophisticated appreciation of predisposing (constitutional and prior life-experience) factors and precipitating factors triggering dysfunction, and factors maintaining SD. Finally, sex therapists are skilled in using cognitive–behavioral techniques for relapse prevention. All of these issues have an impact on the potential capacity for successful restoration of sexual health.

A sex therapist’s perspective

What is the sex therapist’s perspective? Patients who have SD based on deep-seated psychosocial and emotional issues may not be amenable to simple single-agent pharmacologic therapeutics, while patients who have physical issues related to age or illness are unlikely to be fully helped by sex counseling exclusively. Sex therapists working together with physicians who prescribe pharmacologic agents may be able to help patients previously untreated by counseling methods alone. Reciprocally, counseling will help a physician optimize the efficacy of pharmaceutical treatments within the context of an individual patient’s own STP matrix.

Occasionally, the ED patient consults a sex therapist first, who then refers to the physician for evaluation and treatment of organic components of the patient’s ED. Given the tremendous success of pharmaceutical advertising in driving patients

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**Figure 40.2** The elegant solution for ED. ©2006 Michael A Perelman, PhD, from reference 4.
to seek treatment from their PCP, this scenario is now infrequent. When the patient expects the sex therapist to ‘captain’ the treatment, the physician will often prescribe a phosphodiesterase type 5 inhibitor, but only function adjunctively. What is the perspective of the sex therapist in such a situation, where the patient has usually presumed there was a preponderance of psychosocial–cultural etiology. Sex therapists must embrace knowledge gleaned from colleagues in urology, endocrinology, neurology, cardiology, gynecology, primary care, and family practice with the same enthusiastic fervor with which we chastised them earlier for not appreciating our wisdom. Most sex therapists recognize and appreciate the advances in biology, gene therapy, pharmaceuticals, and other areas of medical science. We are beginning to unite behind a new Integrated Sex Therapy (Figure 40.2).

Sex therapists need to embrace our unique ability to manage complex matrices of variables, which dynamically shift the sexual equilibrium. This requires more time than the typical prescribers of sexual pharmaceutical agents have available during an office visit. Fortunately, thoughtful examination and sustained effort while still appreciating treatment duration is part of the sex therapist’s legacy. Sex therapists have multiple roles as educators and counselors, but our identity will be re-stabilized and enhanced by our unique ability to treat successfully individuals and couples who suffer from more complex PSFCs. There are an extremely high proportion of patients who discontinue pharmaceutical agents prescribed for sexual difficulties. Examining discontinuation and pharmaceutical non-responders provides an emerging opportunity to demonstrate the robust power of an Integrated Sex Therapy to assist patients successfully with sexual concerns when a pharmaceutical monotherapy or polyceutical approach has failed.

Conclusion

A biopsychosocial–cultural model of SD provides a compelling argument for combination treatment integrating sex therapy and sexual pharmaceuticals. Restoration of lasting and satisfying sexual function requires a multidimensional understanding of all of the forces that created the problem, whether a solo physician approach or a multidisciplinary team approach is used. Each clinician needs to evaluate carefully his or her own competence and interests when considering the treatment of a man’s ED, so that regardless of the modality used, the patient receives optimized care. For the most part, neither sex therapy nor medical–surgical interventions alone are sufficient to facilitate lasting improvement and satisfaction for a patient or partner suffering from ED. There will be new medical and surgical treatments in the future and sex therapy can complement all of these approaches. This author is optimistic for a future in which a combination of sex counseling and sexual pharmaceuticals are the normative treatment to restore patient and partner’s sexual function and satisfaction.

REFERENCES

Gene therapy in erectile dysfunction: an update

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Introduction

Gene therapy has undergone significant evolution since the completion of the human genome project and the advent of a new age of molecular medicine. In fact, gene therapy and gene transfer were originally regarded primarily as treatment options for life-threatening diseases such as cancer and other acquired and hereditary disorders with few effective treatment options. For such life-threatening applications, the risk–benefit ratio intrinsic to gene transfer was considered to be acceptable.

However, the recent completion of the first phase I gene transfer trial for erectile dysfunction (ED) has opened up new vistas for the potential application of gene transfer to diseases and disorders that have substantial impact on quality of life. As noted in a recent editorial by Dr Arthur Caplan, ED can be considered a serious medical problem as judged by a variety of relevant criteria. Moreover, it is well established that current treatment options are not effective in all patients, especially patients with moderate-to-severe disease. In this scenario, it can be forcefully argued that gene therapy clearly represents an ethical course of research for the treatment of ED.

Not surprisingly, the increased molecular understanding that has accompanied the genomic technological revolution has provided important benefits for the improved understanding, diagnosis and treatment of ED. Since the seminal preclinical publications in this area of research, many different groups have become involved in the pursuit of gene therapy and transfer as effective treatment modalities for ED. In fact, a Medline search using the text words: ‘gene therapy and erectile dysfunction’ revealed 99 hits, with nearly half of these being review-type articles; all of these reports date from the past decade.

With this backdrop in mind, the goal of this chapter is to provide a timely review of the preclinical strategies and recent clinical safety data that have resulted from this decade-long research effort. In short, the strategies thus far employed have interrogated numerous distinct molecular targets in physiologically relevant erectile pathways. A schematic depiction of the approaches tried thus far is shown in Figure 41.1. Nonetheless the diversity of targets can be grouped into a few more general categories. They are:

- modulators of the nitric oxide (NO)–cGMP–G kinase pathway for provision of improved erectile stimulus;
- neural growth factors for improved neuronal innervations;
- strategies for improved vascularity, to ensure adequate blood flow; and
- modulation of second messengers, receptors, and effectors of arterial and corporal smooth muscle cell tone, to ensure enhanced smooth muscle responses to endogenous stimuli.

The vast majority of work thus far has been directly or indirectly focused on the NO–cGMP–G kinase pathway, given the prominent role that this pathway is known to play in the erectile process. Below, we review each of these, as well as the only clinical data available, that is, gene therapy with the human large-conductance, calcium-sensitive potassium (K) channel (or maxi-K).

Gene therapy strategies that modulate the nitric oxide–cGMP pathway

As evident from numerous laboratory investigations, as well as the clinical success of sildenafil and other phosphodiesterase (PDE) type 5 inhibitors, it is clear that the nitrergic system plays a critical role in the normal erectile process. Thus, the NO synthetic pathway and biochemical cascade seems a logical molecular target for gene therapy. The approaches tried thus far are quite diverse and are reviewed below. The rationale is that increased expression of an important endogenous smooth muscle relaxant–vasodilator will assist with the diminished erectile response (i.e. relaxation) characteristic of ED in many impotent patients.

Gene therapy with nitric oxide synthase isoforms

The strategy thus far has been to target one of the NO synthase (NOS) isoenzymes known to be present in the penis. The rationale for this is that, as elsewhere in the body, NOS is responsible for synthesizing NO from L-arginine and molecular oxygen in the penis. There are three known NOS isoforms, and they have all been targeted:

- neuronal NOS [nNOS; penile neuronal NOS (PnNOS) in rats].
• endothelial NOS (eNOS)\textsuperscript{10,11,17} and
• inducible NOS (iNOS), found in macrophages and smooth muscle cells\textsuperscript{5,14}.

The effects observed with iNOS transfection appear as early as 2 days post-injection\textsuperscript{14} and have now been shown to last for up to 10 days after a single injection\textsuperscript{3}. In both cases, there was a statistically significant increase in the cavernous nerve stimulated intracavernous pressure (ICP) response in animals receiving the gene therapy treatment. Similar observations have been made utilizing an adenovirus (Ad)–eNOS vector (i.e. a physiologically significant effect on the nerve-stimulated ICP response was observed within 1 day of transfection).\textsuperscript{11} Importantly, the pharmacological responses to intracavernous injection of zaprinast (a cGMP PDE inhibitor) and acetylcholine were also enhanced; again, this may indicate that gene therapy can be combined with more traditional forms of pharmacological therapy.\textsuperscript{18} Further supporting this, it was shown that over-expression of eNOS and cGMP in combination with sildenafil significantly increased the peak ICP in the streptozotocin (STZ)–induced diabetic rat.\textsuperscript{18} Moreover, subsequent studies by these same investigators have shown that the duration of Ad/eNOS gene therapy can be extended for up to 5 days (note that longer time points were not examined).\textsuperscript{18} In addition, expression of the reporter gene, beta-galactosidase using the same Ad vector lasted for up to 60 days.

One possible way of enhancing the effect of NO is to inhibit the arginase pathway, since arginase is an enzyme competing with NO for the substrate l-arginine. By using the arginase inhibitor 2(S)-amino-6-boronohexanoic acid together with an adeno-associated virus encoding an antisense sequence to arginase I in the aging B6/129 mouse, Bivalacqua et al. found that endothelial and erectile functions could be improved, as reflected by significant improvements of the responses to cavernous nerve stimulation.\textsuperscript{17} It is known that cGMP-dependent protein kinase 1 (PKG1) is probably the most important effector target for cGMP to mediate its effects on erectile function. Consistent with this supposition, in rats with STZ-induced diabetes and ED, erectile function was enhanced by gene transfer (Ad) of protein kinase 1-alpha.

In recent years, PnNOS (the penile-specific variant of nNOS) was transfected in rats using a ‘gutless’ (i.e. replication incompetent) Ad vector, as well as a plasmid.\textsuperscript{13} The main goal of these studies was two-fold:

• to increase transfection efficiency and reduce the immunogenic potential by using a modified Ad vector; and
• to reduce the required viral load by increasing the transfection efficiency with electroporation techniques.

Comparisons with naked DNA plasmids were made in parallel. In these studies, statistically significant, and apparently physiologically relevant, in vivo effects were observed for up to 18 days after a single injection of either plasmid–PnNOS or Ad–PnNOS (i.e. elevated nerve stimulated ICP responses were observed). Furthermore, expression of the beta-galactosidase reporter gene was observed for up to 56 and 60 days post-injection with plasmid and Ad, respectively. Thus, electroporation (i.e. application of electrical current across the injection site) was shown to increase both the apparent transfection efficiency and the duration of the effect of both plasmid and adenoviral-mediated gene transfer techniques.

The main limitation to these studies with NOS gene transfer may well be the relatively short duration of the physiological effect, although it appears that the in vivo effects may be significant at later time points with a greater number of experimental observations (i.e. up to 30 days, consistent with the statistical significance of the beta-galactosidase expression data).\textsuperscript{13} The explanation for the relatively short duration of efficacy is undetermined, but may be related to either the presence of even the ‘gutless’ viral vector or perhaps tight...
cellular regulation of the gene product. While no adverse immunologic, histologic or circulatory effects were observed, the potential long-term side effects of over-expression of the pleiotropic cytokine product (i.e. NO) are not known. Lastly, the possibility of priapism seems to be a real concern with this approach, particularly with respect to iNOS (see Table 41.1).

### Superoxide dismutase gene therapy for ED

Another gene transfer approach may provide a solution for the reduced NO bioavailability that may contribute to age-related ED as a result of enhanced inactivation of NO by oxidative stress in the aging penis.\[19\]-[23] Although NO is rapidly diffusible from nerves or endothelial cells to the neighboring smooth muscle cells for the induction of smooth muscle relaxation, it can be scavenged by its interaction with superoxide anion (O$_2^-$) within vessel walls or corporal sinusoids to form the toxic molecule peroxynitrite (ONOO$^-$).\[22\],[23] The increased levels of O$_2^-$ in the endothelium and smooth muscle of aging corpora cavernosa may cause the decrease in NO bioavailability observed in the aging penis. To test this hypothesis, Bivalacqua et al. examined the effect of adenoviral gene transfer of extracellular (EC) superoxide dismutase (SOD) to the penis on O$_2^-$ levels and erectile function in the aged rat.

| Table 41.1 Summary of published preclinical gene therapy studies in rats |
|------------------------|-----------------|-----------------|-----------------|
| Vector used            | Gene target     | Physiological end-points                  | Duration of effect$^c$ |
| Adenovirus$^5$         | iNOS            | Increased ICP to NS                       | At least 10 days      |
| Adenovirus$^{14}$      | iNOS            | Increased ICP to NS                       | 2 days                |
| Adeno-myoblast$^{14}$  | iNOS            | Increased resting ICP                     |                       |
| Adenovirus$^{33}$      | pNOS            | Increased ICP to NS                       | ≤18 days              |
| Plasmid$^{33}$         | pNOS            | Increased ICP to NS                       | ≤18 days              |
| Adenovirus$^{11}$      | eNOS            | Increased ICP to NS, Ach and Zapranist    | 1 day                 |
| Adenovirus$^{10}$      | eNOS            | Increased ICP to NS                       | 5 days                |
| Adenovirus$^{18}$      | eNOS+sildenafil | Increased ICP to NS                       |                       |
| Adenovirus$^{42}$      | eNOS+mesenchymal stem cells | Increased ICP to NS               | 21 days              |
| Adenovirus$^{32}$      | VEGF            | Increased ICP to NS                       | 8 weeks               |
| Adenovirus$^{33}$      | Ang1+VEGF165    | Increased ICP to NS                       | 8 weeks               |
| Adeno-associated virus$^{31}$ | VEGF+AAV-BDNF  | Increased ICP to NS                       | 4 months              |
| Adeno-associated virus$^8$ | BDNF           | Increased ICP to NS                       | 8 weeks               |
| Herpes simplex$^{26}$  | GDNF            | Increased ICP to NS/BP to NS              | 4 weeks               |
| Herpes simplex$^{27}$  | NT3             | Increased ICP to NS                       |                       |
| Adeno-associated virus$^{12}$ | Rho A        | Increased resting ICP, ICP to NS          | 1 week                |
| Adenovirus$^9$         | cGMP            | Increased ICP to NS                       | 5 days                |
| Naked DNA pc DNA 3.1$^{2,4,40,42}$ | hSlo (maxi-K channel) | Increased ICP to NS          | ≥3–4 months$^a$      |
| cDNA$^{40}$            | K$_{ATP}$ channel | Increased ICP to NS                  | 1 week                |
| cDNA$^{15}$            | VIP             | Increased ICP to NS                       | ≥ 2 weeks             |
| Antisense oligonucleotides$^7$ | PDE V        | Increased cGMP in cultured human corporal smooth muscle cells | ≤1-6 h |
| Adenovirus$^{19}$      | SOD             | Increased SOD activity and cGMP levels    | 1 day                 |

ICP, intracavernous pressure response; NS, nerve stimulation; Ach, acetylcholine; DCNF, brain-derived neurotrophic factor; cGMP, cyclic guanosine monophosphate; iNOS, inducible nitric oxide synthase; pNOS, penile NOS; eNOS, endothelial NO synthase; VEGF, vascular endothelial-derived growth factor; Ang1, angiotensin 1; AAV–BDNF, adeno-associated virus–brain derived neurotrophic factor; BDNF, brain-derived neurotrophic factors; NT3, neurotrophin 3; VIP, vasoactive intestinal peptide, PDE phosphodiesterase; SOD, superoxide dismutase.

$^a$Duration of effect refers to the latest time point at which a physiologically significant increase in the ICP response was measured.

$^b$The most recent data from our group indicate that the physiological effect on ICP lasts for up to 6 months in the aged rat model, and up to 4 months in an experimentally diabetic rat model. Also note that an increased ICP to NS refers to a statistically significant increase over that observed in an untreated age-matched control rat. In general, the responses observed in the gene therapy treated rats were similar to those observed in young animals.
Intracavernosal injection of Ad–cytomegalovirus (CMV) EC-SOD (an adenoviral vector containing the EC-SOD under the control of CMV promoter) into aged rats resulted in a significant increase in erectile responses to cavernosal nerve stimulation, acetylcholine, and zincprazin to a magnitude similar to young rats.\(^9\) In vivo adenoviral gene transfer of EC-SOD to the penis resulted in higher expression of EC-SOD mRNA and protein, higher SOD activity and cGMP levels, and lower nitrotyrosine staining.

These data provide evidence in support of the hypothesis that ED associated with aging is related in part to an increase in cavernosal \(O_2^-\) formation. Intracavernosal EC-SOD gene transfer reduces \(O_2^-\) formation, restores age-associated erectile function and may represent a novel therapeutic strategy for the treatment of ED.\(^8\)

### Antisense oligonucleotide therapy with phosphodiesterase type 5

A study was published in Chinese in 2002 indicating that transfection of cultured human corporal smooth muscle cells with antisense oligonucleotides might also be possible.\(^7\) While the critique of this entire paper is limited here to the abstract, it seems worth including in this review, because of its potential implications to the field. In that regard, antisense oligonucleotides directed to the PDE-5 isozymes was used. The rationale is that the antisense oligonucleotides will base-pair with or bind to the PDE-5 mRNA and prevent translation of the protein. If true, this strategy would be expected to reduce the amount of the PDE-5 isozyme available and, therefore, to increase the half-life of cGMP. Consistent with such a possibility, the authors reported increased cGMP accumulation levels 1–6 hours after transfection, as detected with an enzyme-linked immunosorbent assay (ELISA).\(^7\) Another study was recently conducted evaluating the value of pSilencer2.1-U6-PIN-shRNA gene therapy and concluded that it was more effective than the antisense protein inhibitor of NOS (PIN) mRNA in ameliorating ED in the aged rat, thereby suggesting that PIN is indeed a physiological inhibitor of nNOS and nitricergic neurotransmission in the penis.\(^24\)

### Gene therapy with neurotrophic factors

The concept behind this therapeutic approach is that increasing the number of nerves, and thereby altering the supply side of the erectile effector equation, will restore erectile capacity. This approach would be of specific interest to address neuropathic changes that accompany age, diabetes, or radical prostatectomy surgery. Lue et al. examined the ability of brain-derived neurotrophic factor (BDNF) gene therapy to restore the cavernous nerve-stimulated ICP response in a rat model of neurogenic impotence.\(^8\) After undergoing a bilateral nerve-damage procedure (i.e. nerve freezing), rats received an intracavernous injection of adeno-associated virus (AAV) vector containing the BDNF gene. At 4 and 8 weeks post-injection, rats were examined in functional studies, and corporal tissue was harvested for histological analysis.

Briefly, these studies demonstrate that the AAV–BDNF treated group had a significantly elevated nerve stimulate ICP response, which correlated with a significant increase in the number of NOS-positive nerve fibers observed. However, it should be pointed out that the time course and magnitude of the measured ICP response was relatively modest or blunted (50–60cmH\(_2\)O), compared with that observed in the other gene therapy studies reported in this chapter (which were generally more immediate and in the 60–100cmH\(_2\)O range). This may be a reflection of the intrinsic complexities of neuronal regrowth, and it is conceivable that the magnitude of the increase in ICP may not be sufficient to produce an erection in this model. Nonetheless, these important initial studies do open the door to the possibility of affecting the ‘driving force’ for erection by manipulating the innervation density. Such a possibility has been previously documented on both theoretical and practical grounds,\(^8\) and it would represent a real step forward in the understanding and treatment of ED.\(^26,27\)

Kato et al. used gene transfer with herpes simplex virus vector (HSV) expressing gial-cell-line-derived neurotrophic factor (GDNF) in rats in which the cavernous nerve was bilaterally injured using a clamp and dry ice.\(^26\) They found that at 4 weeks after nerve injury, rats treated with HSV–GDNF had a significant recovery of erectile function compared with rats treated with control vector or untreated rats. The same HSV was used by Bennett et al. to deliver neurotrophin-3 (NT3) to rats with STZ-induced diabetes and ED.\(^27\) They found that NT3 vector injected directly into the cavernous nerve sheath increased the mean number of nNOS-positive neurons and produced a significant increase in the maximal ICP induced by electrical stimulation of the cavernous nerve, and they concluded that NT3 gene therapy may be applicable for the treatment of diabetes-associated ED.

### Strategies for improved vascularity: gene therapy with vascular endothelial-derived growth factor

An insufficient vascular supply is thought to be responsible, at least in part, for the etiology of some ED. While it seems that in many cases, sufficient corporal smooth muscle relaxation (i.e. intracavernous injections) can overcome this deficit, nonetheless there is a rational basis for expecting that an increased blood flow will aid recovery of erectile function and capacity. Thus, the strategy here is to use an angiogenesis strategy to increase the vascularity of the penis to provide an increased blood flow component to the erectile process. While the number of patients whose ED is solely related to decreased vascularity may be small, a technique that could produce more subtle increases in vascularity might prove to be prophylactic. Moreover, this approach is also quite distinct from those described above, and is therefore worthy of consideration. In fact, vascular endothelial-derived growth factor (VEGF) gene transfer techniques are currently being applied to the treatment of other ischemic cardiovascular diseases such as myocardial ischemia.\(^28\)
In addition, another recent study has characterized the VEGF isoforms present in the corpora of humans and rats. Furthermore, consistent with the aforementioned observations, the direct intracorporeal injection of VEGF in a rat model of vascular insufficiency had restorative effects on the nerve-stimulated ICP response, and has clearly provided ‘proof of concept’ for this approach.

However, Dr Lue and colleagues were the first to provide preclinical data supporting a potential role for VEGF gene transfer to the amelioration of ED. In two different studies, the San Francisco group illustrated the ability of an AAV–VEGF construct to mitigate the degree of ED observed in rodent models of atherosclerosis and veno-occlusive dysfunction. In both instances, intracavernous injection of AAV–VEGF was associated with detectable remodeling of the penile erectile tissue, and corresponding enhancements in the cavernous nerve stimulated ICP response (Table 41.1).

In another recent study, Ryu et al. showed that combination gene transfer with angiogenic factors, in this case, angiopoietin-1 and VEGF, may provide an even more favorable outcome for the treatment of atherosclerosis-related ED. While details of the time course and magnitude of the increased or altered vascularity observed at the histological level are still lacking, taken together these data are consistent with the supposition that gene-based approaches using angiogenic factors may be useful in the treatment of ED. The potential pleiotropic actions of this cytokine on multiple cell types (as mentioned for NO above) may provide a significant clinical barrier. Certainly then, this would also be considered to be in the supply-side category of gene transfer techniques.

Modulation of second messengers, receptors, and effectors of arterial and corporal smooth muscle cell tone: gene therapy with modulators of the cAMP pathway

While NO is clearly a major modulator of erectile capacity and function in the normal penis, it is well known that other vasorelaxants are also present and potentially relevant to erectile function. Among the possible suspects, calcitonin gene-related peptide (CGRP) has long been hypothesized to be such a compound. CGRP is an effector of erectile capacity by virtue of its ability to produce a receptor-mediated increase in intracellular cAMP levels, and a concomitant cellular hyperpolarization via increased K+ channel activity. The therapeutic rationale applied here is similar to that described above for the NO cascade, and involves increasing expression of CGRP in order to enhance the cAMP-mediated relaxation response in aged rats, thus ameliorating the age-related decline in the nerve-stimulated ICP response. Using an adenoviral-mediated delivery system, Bivalacqua et al. were able to document that over-expression of CGRP reversed the age-related decline in CGRP and cAMP concentrations in the rat corpora, and moreover, produced an increase in the nerve-stimulated ICP response to a level equivalent to that of young animals. This effect lasted for up to 5 days, although longer time points were not examined. As such, the precise duration of the effects of this therapy is unknown, but it nonetheless appears that this may represent an attractive therapeutic possibility. The potential long-term side-effects, if any, are also not known. Importantly, there were no detectable effects of CGRP over-expression on rest or ICP or blood pressure in this series of experiments.

Vasoactive intestinal polypeptide (VIP) is another endogenous smooth muscle cell relaxing agent that has long been thought to be a potentially important neurotransmitter for penile erection. In a recent investigation Shen et al. injected pcDNA3/VIP naked DNA intracorporally in STZ-diabetic rats after 10 weeks of established diabetes. In short, the nerve-stimulated ICP responses were significantly elevated in the STZ-diabetic rats that received the VIP DNA to levels that appear sufficient to restore penile erection in this animal model. Importantly, elevated levels of VIP were found only in the penile erectile tissue, and not in liver, kidney, or aorta. These effects lasted up to 14 days post-injection, the last time point examined. Taken together, these two preclinical studies certainly document that modulation of the cAMP pathway is also a potentially effective strategy for the treatment of ED.

Gene therapy of RhoA: alterations in calcium sensitization

Calcium sensitization refers to the ability of corporal smooth muscle cells to maintain a tonic contraction in the face of near-resting intracellular calcium levels. Presumably the RhoA–Rho-kinase pathway plays a major role in this process. In fact, calcium-sensitization mechanisms represent an important component to the tonic contraction of corporal smooth muscle, and thus, flaccidity. In a first attempt to target this system using gene-based approaches, the investigators transfected the corpora with a dominant-negative mutant of RhoA. The goal was to increase competition between the endogenously expressed RhoA isoforms and the nonfunctional RhoA mutant. In these studies both endogenous RhoA and Rho-kinase expression were unaltered by the presence of the RhoA mutant. As expected, transfection with the RhoA mutant using an AAV vector (see Table 41.1 for details) was associated with a decreased phosphorylation of the regulatory subunit of the myosin light-chain phosphatase, consistent with a decrease in calcium sensitization (i.e. an inhibition of an inhibition), nominally anticipated to produce a lower degree of corporal smooth muscle cell tone. In line with the suspected mechanism of action, there was an approximately two-fold increase in basal ICP and, moreover, a significant increase in the cavernous nerve-stimulated ICP response (the ICP: blood pressure ratio approximated unity at the highest levels of stimulation). No effects were observed on mean arterial pressure, and there was no evidence of an inflammatory response or other side-effects at the 1-week time point in these initial studies. The efficacy and side-effect profile of longer time points are currently unknown. Nonetheless, this report
Gene therapy with potassium channels

K+ channels provide an important mechanism for the regulation of corporal smooth muscle cell tone and, moreover, represent a convergence point for mediating the effects of a wide array of endogenous neurotransmitters, neuromodulators, and hormones. Thus, K+ channels represent an attractive therapeutic target for the treatment of ED. Thus far the majority of data and efforts derive from gene transfer with the alpha-, or pore-forming, subunit of the human large conductance, calcium-sensitive K+ channel (K_a alpha-subunit or maxi-K channel), referred to here as hSlo. In this regard, while the K_a channel represents the primary focus of our efforts to date, unpublished data from our group also indicate that gene transfer with the alpha-subunit of another important K+ channel subtype, namely Kir6.2, might also restore diminished erectile capacity in the aged rat model.

Consistent with this supposition, another recent report has also utilized a similar strategy with the metabolically regulated K+ channel (i.e. K_ACT). The rationale behind ion channel gene therapy is based on the tight link between K+ channel activity, transmembrane calcium flux through voltage-dependent calcium channels, and corporal smooth muscle cell tone. Specifically, over-expression of hSlo in corporal smooth muscle cells is presumed to increase the hyperpolarizing ability of the syncytial corporal smooth muscle cell network, and by so doing, increase the responsiveness of the erectile apparatus to a nominally diminished supply of endogenous smooth muscle relaxants (a similar rationale would apply to the K_ACT channel). In any case, the physiological end-point is restoration of a degree of corporal smooth muscle relaxation sufficient to result in normal penile erection. The evidence consistent with this supposition has been recently reviewed. Of note is the fact that the gene product, namely, the maxi-K channel, apparently exhibits little or no activity in the corporal smooth muscle cell during flaccidity but becomes robustly activated by the endogenous erectile second messenger pathways during tumescence.

Consistent with the fact that hSlo has little impact on baseline corporal smooth muscle activity, no evidence for the possibility of priapism (i.e. increased resting ICP) has been observed in our preclinical work to date, nor in the recently completed phase 1 clinical trial. Moreover, as with other gene therapy approaches discussed in this chapter, there is apparently no pathologic effect on corporal tissue histology or architecture (i.e. no inflammatory or immune response), or on mean arterial blood pressure. Another advantage of this gene therapy approach is the apparent longevity of exogenous gene expression. Published reports indicate that the physiologic effects of a single intracorporal injection of hSlo–pcDNA (‘naked DNA’) can last for up to 4–6 months.

Cell-based gene therapy

All of the approaches described thus far involve genetically modifying the extant cells in the corpora. Another possibility is the re-implantation of genetically modified cells into the corpus cavernosum. The strategy here is to ‘seed’ the penis with cells having the desired, genetically modified, physiological characteristics. Wessells and Williams have established the feasibility of utilizing autologous transplantation of endothelial cells into the corpus cavernosum of the rat. The next step would be to endow these cells with the desired genetic characteristics ex vivo, prior to their re-implantation in vivo. A similar approach, also in the rat model, has documented the feasibility of using iNOS adenoviral-transfected myoblasts as the delivery vehicle. In this latter instance, increases in the nerve-stimulated ICP response were observed (Table 41.1). In this scenario, the newly seeded cells provide an additional reservoir or supply of endogenous vasorelaxants. With the currently contemplated approaches then, the end-result should be a diminished baseline corporal smooth muscle cell tone or an enhanced supply of vasorelaxants (or both).

Bivalacqua et al. have shown the same experience with cell-based therapy utilizing the endothelial cells both alone and ex vivo gene modified with eNOS. They illustrated that the results obtained from both techniques were statistically better than controls up to 21 days post-transplantation; however, the ex vivo modified cells have shown improvement to the erectile function as early as 7 days post-transplantation. Most recently, intracavernous injection of e-NOS-modified syngeneic rat mesenchymal stem cells (bone marrow) was documented to improve the erectile response in aged rats at 7 days and 21 days after injection. This increase in erectile function was associated with increased eNOS protein, NOS activity, and cGMP levels. These results suggest that combining the cell-based therapy and gene transfer therapy may be a suitable alternative for future work.

Questions remain concerning the long-term viability of autologously transplanted cells in the corpus cavernosum. Certainly, this is another exciting approach that would open up additional therapeutic possibilities, and would fall into the supply-side category of gene transfer techniques.

Human clinical data

The ultimate goal of all of these approaches is to apply the findings to improve the treatment of ED in humans. In this regard, the first human clinical trial of gene transfer for the treatment of ED has recently been completed. In this seminal dose-escalation safety study 11 patients with moderate-to-severe ED were given a single-dose corpus cavernosum injection of hMaxi-K, a ‘naked’ DNA plasmid carrying the human cDNA encoding hSlo (for human slow-poke), the gene for the alpha-, or pore-forming, subunit of the human smooth muscle maxi-K channel. More specifically, 3 patients were each given hMaxi-K 500 μg, 1000 μg, and 5000 μg, and 2 patients were given hMaxi-K 7500 μg, and followed for 6 months. As always, the primary end-point of this phase I study was safety. Importantly, no serious adverse events or
dose-related adverse events attributed to gene transfer were observed for any patient at any dose during any study visit. Moreover, no clinically significant changes from baseline were seen in physical evaluations (general and genitourinary) or in hematology, chemistry, or hormone analyses. There were no cardiac events, as determined by repeated electrocardiograms, and no plasmid was detected in the semen of patients at any time after the injections. In addition, secondary efficacy end-points were measured using the International Index of Erectile Function (IIEF) scale, with patient responses validated by partner responses. In this regard, one patient at each of the two highest doses of hMaxi-K (i.e. 5000 µg and 7500 µg doses) had apparently sustained improvements in erectile function as indicated by improved IIEF erectile function domain scores over the length of the study. In fact, these patients reported erectile function category improvements that were highly clinically significant and maintained throughout the 24 weeks of study. While efficacy conclusions cannot be drawn from results of a phase 1 trial without a control group, these initial safety data are indeed encouraging and, furthermore, these indications, albeit preliminary, of effectiveness suggest that hMaxi-K gene transfer may be a viable approach to the treatment of ED. Clearly further clinical investigation is both required and justified. Nonetheless, these exciting data represent a major step toward bringing the age of molecular medicine to bear on the treatment of ED.

Conclusion

Clearly, all of the preclinical data collected to date are very encouraging, and the work of Melman and colleagues is equally ground breaking and encouraging in the clinical arena. As one looks to the future, from a clinical standpoint, some of the major advantages of further advancing gene-based treatments for ED are:

- the potential for restoration of normal organ function in the absence of the necessity for any other form of therapy;
- elimination of the need to ‘plan’ for sex (i.e. it would represent an ‘on-demand’ therapy); and
- the possibility of combination therapy with currently existing pharmacological approaches.

This approach would reduce the required doses of oral medications, thus increasing their efficacy and nominally decreasing their side effect profile.

As discussed in detail elsewhere, for any and all of the aforementioned reasons, the continued preclinical and clinical success of gene therapy and transfer would represent a huge step forward in the treatment of ED in particular.

Lastly, the success of any gene therapy protocol would open the door to the possibility of new treatments for a wide range of human smooth muscle disorders (e.g. urinary incontinence, irritable bowel disorders, asthma, premature labor).

REFERENCES


Stem and endothelial progenitor cells in erectile biology: future therapeutic applications and potential biomarker for erectile dysfunction

Trinity J Bivalacqua, Travis D Strong, Hunter C Champion, and Arthur L Burnett

Background

The Massachusetts Male Aging Study (MMAS), a substantial epidemiological survey that quantified the prevalence of erectile dysfunction (ED) in a non-institutionalized population of men in the Boston area, revealed that 52% of 1290 men aged 40–70 years had some degree of ED. Additional studies have estimated that the worldwide incidence of ED will increase from 152 million men in 1995 to 322 million men by the year 2025. Vascular disease is a major cause of ED, and several cardiovascular risk factors such as smoking, aging, hyperlipidemia, diabetes, and hypertension are strongly correlated to ED. Injury to the cavernous nerves during pelvic surgeries (e.g. radical prostatectomy, radical cystoprostatectomy) is the cause of an appreciable number of ED cases as well.

In order to achieve penile tumescence, smooth muscle within the corporal sinusoids must relax and dilate. In the flaccid state, the contractile machinery of penile smooth muscle is tonically activated, thus decreasing luminal space and prohibiting engorgement. Nitric oxide (NO) is now understood to be a key mediator in diminishing penile smooth muscle tone by increasing the production of cGMP (Figure 42.1). In turn, cGMP activates a cGMP-dependent protein kinase (PKG), which phosphorylates and activates downstream promoters of vasodilatation. Upon neurogenic stimulation, NO is released from nitricic axons and acts to initiate an erection. As engorgement begins, shear stress within the penile vasculature activates the production of endothelial-derived NO, a critical component in the maintenance of erection.

Basic science research on erectile physiology has focused on the pathogenesis of ED and has provided convincing evidence that ED is predominately a disease of vascular etiology. Phosphodiesterase (PDE) type 5 inhibitors are first-line pharmacotherapies for the treatment of ED because of their high efficacy rate in a diverse population of patients. Although PDE-5 inhibitors are effective, these oral medications have failed in certain disease states, such as diabetes, post-prostatectomy ED, and severe vascular dysfunction. This has resulted in the development of new approaches, including gene and cell-based therapies for the treatment of ED. Therapeutic strategies for ED that aim at rejuvenating dysfunctional cells (endothelium) or replacing lost or critically damaged cells (nerves, smooth muscle) would be of immense value. Additionally, early diagnosis with the use of biomarkers for high-risk ED patients has been advocated in order to select patients that are at greatest risk for cardiovascular disease as well as patients who would benefit most from PDE-5 inhibitor therapy.

Fundamentals of cell-based therapies for erectile dysfunction

The long-term goal for the treatment of any disease process is to identify molecular correlates involved in the pathophysiology of disease, and use this information to develop novel and more effective therapeutics. Gene and cell-based therapies provide attractive therapeutic possibilities for the treatment of ED because selective genes of interest that are involved in neural degeneration and penile vascular dysfunction can be targeted. In most men only a small alteration in the balance between contracting and relaxing stimuli can cause significant effects on corporal and penile vascular smooth muscle tone. Thus, transfer of a therapeutic gene product into the penis via non-viral and viral vectors, as well as cells alone or genes modified ex vivo, may restore impaired erectile function. Using gene and cell-based therapies, erectile function can be modulated and potentially restored by altering the physiological supply and demand of the erectile apparatus.

Recently, the emerging concept of the use of stem cells for the treatment of severe neurogenic and penile vascular dysfunction has gained substantial attention. This approach has so far yielded encouraging results for treating both vasculogenic and neurogenic ED. By rejuvenating or replacing defective penile tissues with stem cells, it is conceivable that cell-based therapies could result in permanent
functional restoration. Such a potential outcome stands in stark contrast to current therapies, which require continuous intervention. Stem cell-based therapy may also offer an option for those men with presentations of ED unresponsive to currently available medications (PDE-5 non-responders).

Definition of stem cells

Because cell senescence and degeneration increases with time, older people are acutely prone to cell loss and consequent disease. In this cell population, pharmacological agents may be largely ineffectual at stimulating the inherent regenerative capacity of the failing tissue. It is evident that in many conditions an alternative to drug therapy is needed, which focuses on the transplantation of healthy donor cells or the restoration of tissue-resident stem cells, which may then repopulate and functionally improve compromised tissues.

Stem cells are by definition capable of self-renewal, differentiation into one or more phenotypes, and functional reproduction of the damaged tissue. The differentiation capacity of stem cells falls along a gradient of potency. Restricted to early development, totipotent cells are those with the capacity to differentiate into not only all the cells of an organism, but also the extra-embryonic tissues. Pluripotent stem cells are capable of giving rise to every cell phenotype of the adult, thus comprising all three embryonic layers: endoderm, mesoderm, and ectoderm. Embryonic stem cells are the most widely acknowledged example of pluripotent cells. Lineage-restricted potency (and loss of unlimited self-renewal) is a feature of multipotent, tissue-resident stem cells such as hematopoietic stem cells residing in the bone marrow. With yet more limited differentiation potential, the term ‘progenitor cells’ is loosely used in the literature to refer to cells capable of becoming one or a small number of related cells.

Definition of endothelial progenitor cells

In 1997, the apparent detection of endothelial progenitor cells (EPCs) circulating within human blood was identified. Asahara et al. showed that under specific culturing conditions peripheral blood mononuclear cells (PBMCs) enriched for CD34 could ostensibly differentiate into endothelial-like cells. Consistent with mature endothelial cells, these cells expressed the endothelial markers CD31, CD34, vascular endothelial growth factor receptor 2 (VEGFR2, Tie-2), and eNOS and formed vessel-like structures in Matrigel. These data suggested the existence of a population of circulating, bone-marrow-derived (BMD) cells that can differentiate into mature endothelial cells under particular stimuli.

By methods that are still becoming elucidated, BMD EPCs are stimulated by various cytokines to emigrate from the bone marrow to sites of tissue stress such as occurs in hypoxia. Within the hypoxic vasculature, EPCs bind to the endothelium in an antigen-dependent manner and secrete angiogenic factors, incorporate themselves within the endothelium, or perhaps extravasate into the extracellular matrix and form blood vessels de novo. The discovery of EPCs circulating within the blood spurred a very rapid, and greatly premature to some, advancement to clinical trials. A litany of clinical trials has provided evidence that either unfiltered PBMCs or PBMCs enriched for EPC characteristics can, in some cases, increase neoangiogenesis, improve endothelial function, and positively affect clinical outcomes. Since ED is often a manifestation of endothelial dysfunction in the penis, the use of EPC as a therapeutic intervention or as a potential biomarker has been advocated (see below).

Preclinical evidence for the use of cell-based therapies for vasculogenic erectile dysfunction

Gene therapy, although effective in animal models of ED as a more lasting approach, carries substantial risks of random transgene expression and inflammatory effects. As a result, the most likely application for gene-based therapies may be the ex vivo manipulation of cells prior to transplantation. Gene- and cell-based therapies may thus act synergistically. With or without concurrent genetic modifications, cell-based approaches may offer significant benefits over both in vivo gene therapy and pharmacological agents (Table 42.1).

Cell-based therapies can be used to replace dysfunctional or dying cells in a way that may obviate the need to comprehend the subtle pathological deviations in molecular pathways
leading to ED. To a significant degree, cell-based therapies treat comprehensive molecular pathologies of the damaged tissue, and therefore an understanding of the precise nature of the dysfunction may not be critical. The new cells, being functional simulacra to the healthy native tissue, will conceivably take over the proper function of the damaged cells. In the case of ED, these cells could functionally replace damaged endothelial cells, smooth muscle cells, or neurons. Clearly, it is an oversimplification to discount the need to probe the molecular underpinnings of ED, but much of the promise of cell-based therapies lies in their well-documented abilities either to wholly replace damaged cells or to secrete factors in a paracrine fashion that somehow repair dysfunctional cells, seemingly irrespective of the specific pathophysiology. Although stem cell-based approaches for treating ED are new, the few pioneering studies have reported very promising results, some documenting long-term functional improvement (Table 42.2). Reviewed below are the known studies that have explored the potential for using stem or progenitor cells in the treatment of ED (Figure 42.2).

The natural aging process and diseases of the cardiovascular system (such as diabetes, hypertension, hypercholesterolemia, dyslipidemia, and atherosclerosis) greatly increase the risk of vasculogenic ED.\(^\text{1-4}\) The systemic vasculature is frequently taxed by endothelial dysfunction, a complex condition that may not be fully reversible through treatment with pharmacological agents. In patients with hypertension and atherosclerosis, endothelial dysfunction of the penile vasculature is often the primary cause of ED.\(^\text{35,36}\) If the penile endothelial cells are compromised, then replacing these cells with stem or progenitor cells may be a viable therapeutic option. Two stem or progenitor cell populations – mesenchymal stem cells and endothelial progenitor cells – have been evaluated for either treating or predicting vasculogenic ED.

### Mesenchymal stem cells

Mesenchymal stem cells (MSCs) are intermixed within the bone marrow stroma in a sparse population of multipotent stem cells with the unique capacity to differentiate into mesodermal tissues such as osteoblasts, chondrocytes, and adipocytes.\(^\text{37}\) MSCs have the additional ability of differentiating into non-mesodermal phenotypes such as neurons, lung epithelial cells, and hepatocytes.\(^\text{38-40}\) MSCs have been isolated in a number of other tissues and organs, including placenta, cord blood, and adipose tissue.\(^\text{41}\) The presence of MSCs in a

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### Table 42.1 Comparisons among current treatment strategies for erectile dysfunction

<table>
<thead>
<tr>
<th>Pharmacotherapy</th>
<th>Gene therapy</th>
<th>Cell-based therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>Effective in animal models</td>
<td>Effective in animal models</td>
</tr>
<tr>
<td>Duration of effect</td>
<td>Moderate duration (weeks to months)</td>
<td>Potentially extensive duration (months to years)</td>
</tr>
<tr>
<td>Invasiveness</td>
<td>Intracavernous or intravenous delivery</td>
<td>Unregulated cell division; unintended phenotypic differentiation</td>
</tr>
<tr>
<td>Risks</td>
<td>Random transgene expression; inflammatory response</td>
<td></td>
</tr>
<tr>
<td>Relatively minor</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 42.2 Summary of recent efforts involving stem cell treatment for erectile dysfunction

<table>
<thead>
<tr>
<th>Stem cell type and reference</th>
<th>Source of cells</th>
<th>Model of erectile dysfunction</th>
<th>Donor cell differentiation</th>
<th>Functional improvement?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neural embryonic stem cells(^\text{16})</td>
<td>Syngeneic embryonic stem cells</td>
<td>Bilateral cavernosal nerve crush in rats</td>
<td>Not determined, but neurons suspected</td>
<td>Yes (3 months)</td>
</tr>
<tr>
<td>Muscle-derived stem cells(^\text{17})</td>
<td>Skeletal muscle of syngeneic females</td>
<td>Bilateral cavernosal nerve transaction in rats</td>
<td>Not determined, but donor cells found in smooth muscle</td>
<td>Yes (2 and 4 weeks)</td>
</tr>
<tr>
<td>Mesenchymal stem cells(^\text{18})</td>
<td>Syngeneic bone marrow</td>
<td>Aged rats</td>
<td>Endothelial, smooth muscle</td>
<td>Yes (1 and 4 weeks)</td>
</tr>
<tr>
<td>Mesenchymal stem cells(^\text{19})</td>
<td>Fetal human spinal vertebrae</td>
<td>None; young, healthy rats</td>
<td>Endothelial, smooth muscle</td>
<td>Not determined</td>
</tr>
</tbody>
</table>
number of different organ systems has led some to contend that these cells may exist within virtually every postnatal organ.  

The combined attributes of multipotency, robust proliferation ex vivo, and amenability to genetic manipulation have inspired many researchers to study the potential clinical applications of MSCs. In animal experiments, MSCs have shown the capacity to home to damaged tissues, and they apparently differentiate into the necessary mature phenotypes. Clinical applications are being presently undertaken or are imminent for several common maladies such as heart disease and neurological diseases (e.g. amyotrophic lateral sclerosis). The method by which MSCs improve the regeneration of various tissues has been ascribed to direct differentiation, fusion into heterokaryons with resident cells, and the release of paracrine growth factors. Allogeneic MSCs can often escape the notice of the immune system because of their lack of HLA class II.  

The documented multipotency, high engraftment, and immune suppression of MSCs make them an intriguing source for cell-based therapy for ED. Given the right environment, MSCs have the established capacity to differentiate into diverse cell types and thus conceivably may be able to replace damaged or dysfunctional tissues of the penis. MSCs can successfully repair vascular diseases and insults in vivo, suggesting the possibility that this stem cell population may be effective in replacing or rejuvenating the dysfunctional analogous tissues within the penis.
Currently, little is known about the effect of MSC-based therapy on erectile physiology. Recently, Bivalacqua et al. assessed the potential for MSCs alone or when transfected with endothelial nitric oxide synthase (eNOS) to differentiate into new endothelial and smooth muscle cells, as well as their effect on penile endothelial-derived NO bioavailability and erectile physiology (see Figure 42.2). Rat MSCs (rMSCs) were isolated, expanded ex vivo, and transfected with eNOS,21,22 Aged rats, known to have diminished NO bioavailability and resultant vasculogenic ED, were injected intracavernosally with vehicle, rMSCs alone (with or without transfected lacZ), or rMSCs transfected with eNOS. Seven and 21 days later, engraftment, differentiation, eNOS expression and activity, and erectile responses were assessed. Seven days following injection of lacZ-transfected rMSCs, rMSCs had adhered to a number of cell types in the penis, including the vascular endothelium and smooth muscle cells. After 21 days, the cells had engrafted within the corporal sinusoids and had begun expressing endothelial and smooth muscle antigens that were not previously expressed in vitro, such as eNOS, CD31, and smooth muscle myosin heavy chain (SM-MHC). Seven days after intracavernous injection, penises obtained from rats transfected with rMSC expressing eNOS had higher levels of eNOS protein/activity compared to vehicle or rMSCs alone. Erectile responses were demonstrably higher in the rats treated with eNOS-transfected rMSCs than vehicle and rMSCs alone. After 21 days penises obtained from rats treated with rMSCS alone and eNOS-transfected rMSCs expressed higher levels of eNOS protein and activity and cGMP compared with vehicle. At both 7 and 21 days, no inflammatory response or fibrosis was documented, highlighting the ability of allogenic rMSCs to modulate the immune response. By mechanistically connecting improved physiological responses and enhanced endothelial-derived NO bioavailability following rMSC injection, this study has provided strong support for the potential therapeutic use of MSCs to treat vasculogenic-related ED by improving endothelial-derived NO biosynthesis in the penis via direct differentiation of the MSCs as well as unknown local paracrine mechanisms.

In the ensuing paper, Song et al. assessed the potential of immortalized human MSCs to differentiate into endothelial and smooth muscle cells within the corpora cavernosa of rats (see Figure 42.2). Human MSCs (hMSCs) were isolated from fetal spinal vertebrae and immortalized through the introduction of the v-myc oncogene. The immortalized human MSCs were injected into the corpora cavernosa of young rats and the corpora cavernosa were collected after 2 weeks. Prior to injection, cultured hMSCs did not express the endothelial markers CD31 and vWF or the smooth muscle markers desmin, calponin, or smooth muscle actin (SMA). Two weeks after injection, however, immunofluorescence revealed that many of the injected hMSCs began expressing the endothelial and smooth muscle cell antigens. This study emphasized the differentiation capacity of hMSCs in young, healthy rats; physiological measurements of erectile function were not collected.

In combination, these early studies suggest that syngeneic and allogeneic MSCs have the capacity to differentiate into endothelial and smooth muscle cells after being injected into the corpora cavernosa of rats. MSC-derived endothelial cells within the corpora cavernosa also appear to be fully functional through the increase in physiological response and relevant molecular markers in an animal model of vasculogenic-related ED. Finally, the lack of immune response suggests the safety of allogeneic MSC cell-based therapy for ED. Further studies are clearly warranted and are ongoing.

Preclinical evidence for the use of cell-based therapies for neurogenic erectile dysfunction

For neurogenic ED caused by iatrogenic intervention (e.g. after radical prostatectomy), trauma, diabetes, or neurological disease, cell-based therapies may offer a novel way of regenerating neural signaling. Chronically axotomized peripheral nerves frequently result in poor regeneration, possibly caused by apoptosis of the involved neurons, Schwann cells, and smooth muscle and endothelial cells. Oral pharmacotherapy is unlikely to resurrect all these tissues effectively. For such scenarios, cell-based therapy may be the most promising approach.

Embryonic stem cells

Embryonic stem cells (ESCs) are pluripotent cells derived from the inner cell mass of blastocysts or from single blastomeres. In the laboratory, ESCs have been coaxed to differentiate into a vast number of mature cells, originating from all three embryonic germ layers, including cardiomyocytes, hepatocytes, endothelial cells, keratinocytes, insulin-secreting cells, and neurons, to name just a few. ESC therapy has lagged, however, partly owing to immunogenicity, the teratogenic risks of transplanting pluripotent cells, and innumerable ethical issues related to harvesting ESCs.

ESCs were the first group of stem cells to be evaluated for treating neurogenic ED associated with cavernous nerve injury (see Figure 42.2). Isolated ESCs from rat blastocysts, which were directed to differentiate into neural embryonic stem cell groups (NESC), were utilized. Three months following NESC injection to the major pelvic ganglion (MPG) or crura, tests of erectile response were performed. After the 3-month interval, erection physiology measurements demonstrated a significant decline in erectile response in bilateral nerve crush groups compared with sham. The experimental groups receiving a NESC injection in either the crura or MPG exhibited significantly improved erectile responses. NESC therapy groups showed significantly higher neurofilament expression compared with vehicle in both the MPG and dorsal cavernous nerve. Crural or MPG injection of NESC yielded no difference between neurofilament expression in the experimental and sham groups in both the MPG and dorsal cavernous nerve. This study revealed that ESCs directed along a neural lineage are able to exert some neuroprotective effects. Whether the NESC differentiated into new neurons, glia, or transiently secreted neurotrophic factors is unknown. The authors could not identify transplanted cells within the cavernosa, suggesting that perhaps these cells acted in a paracrine manner. Additional studies are clearly necessary to determine the mechanisms
involved in neuronal regeneration or protection after ESC-based therapy in models of cavernous nerve injury.

**Muscle-derived stem cells**

When skeletal muscle is enzymatically degraded into its constituent cells, these cells proliferate robustly, maintain long-term self-renewal capability, and express myogenic and stem cell antigens. These early myogenic precursors, termed muscle-derived stem cells (MDSCs), are capable of adopting phenotypes of vastly diverse cell types. In urological tissues, MDSCs have been transplanted with surprising efficacy into the smooth muscle of damaged bladder and urethra, resulting in functional recovery of muscle control and diminished incontinence. Remarkably, the innervation of these tissues improved, suggesting direct differentiation into neural cells or the secretion of neurotrophic factors or both. Recently, Kim et al. isolated MDSCs from skeletal muscle, and these enriched MDSCs were then transfected with lacZ and injected into both corpora cavernosa immediately prior to bilateral cavernosal nerve transaction in a rat model. Rats undergoing sham surgery (bilateral cavernous nerve transaction plus no therapy) demonstrated markedly lower erectile responses as well as decreased cavernosal expression of the pan-neuronal marker PGP 9.5, at 2 and 4 weeks after surgery. Experimental groups receiving bilateral injections of 1 × 10^6 MDSCs (into each corporal body) had demonstrably greater erectile responses and cavernosal protein gene product (PGP) 9.5 expression compared with the sham surgery group. Further histology revealed the presence of lacZ-containing cells integrated within the smooth muscle cells.

The significance of this study is the apparent identification of a readily accessible cell population for cell-based ED therapy. Clearly, this is an intriguing study deserving of further exploration. Owing to their multipotency, not to mention their robust proliferation and high engraftment, MDSCs may prove to be a preferred source for cell-based ED treatment.

In this study, MDSCs assisted in the regeneration of nerves, and the authors concede that it is uncertain exactly how the MDSCs exert their neuroprotective effects, but they offer the possibility of direct differentiation into cells with neuronal phenotypes. Such a finding would be very interesting because MDSCs are primarily used in basic and clinical research for their muscle-regenerating capacity rather than their ability to protect or differentiate into neuronal cells.

There are potential drawbacks to stem cell (MSC, ESC, MDSC)-based therapies for ED. As a general caveat, stem cell treatments hold the risk of unintended differentiation, along with the ensuing complications. If the differentiation pathway is not thoroughly controlled, stem cells injected into the penis may very well differentiate into ectopic fibroblasts or osteoblasts, thus potentially creating a significantly worse situation. As a result, it is critical for the researcher to evaluate such rogue differentiation by determining the presence of unintended phenotypes. In addition, inflammation and graft rejection with allogeneic cells may be a formidable hurdle to overcome. Autologous and allogeneic stem cell approaches to treating ED are likely to differ from each other in several respects, each having unique benefits and drawbacks (Table 42.3). Further research is required to determine in which scenarios one cell source would be a better option than the other.

**Endothelial progenitor cells as potential biomarker for erectile dysfunction**

Innumerable studies have shown strong epidemiological associations between ED and cardiovascular disease, and others have suggested ED as an independent risk factor for major cardiovascular events. Linking ED and cardiovascular disease appears to be the pathological phenomenon of

<table>
<thead>
<tr>
<th>Table 42.3</th>
<th>Comparisons between allogeneic and autologous sources for potential stem cell treatment for erectile dysfunction</th>
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<tbody>
<tr>
<td><strong>Allogeneic (banked centrally)</strong></td>
<td><strong>Autologous</strong></td>
</tr>
</tbody>
</table>
| **Pros** | • Donor cells would be functionally normal (i.e. free from endothelial dysfunction)  
• Demonstrated in animal models to differentiate appropriately and improve erectile physiology  
• Genetic modifications possible  
• Centralized cell bank would provide expedited treatment |
| **Cons** | • Histocompatibility concerns  
• Quality of cells varies by donor  
• Replicative senescence limits extensive expansion  
• Karyotypic and phenotypic changes during growth  
• Unregulated cell growth a possibility, particularly with donor cells derived from ESCs |
| **Pros** | • Histocompatibility effectively guaranteed  
• Certain prospective cell populations may grow robustly ex vivo, providing abundant donor cells in a limited time (e.g. MSCs and late outgrowth EPCs)  
• Genetic modifications possible |
| **Cons** | • Donor cells may be susceptible to original conditions leading to tissue failure  
• Cell extraction potentially difficult and/or painful  
• Lack of viable stem cells in those populations most in need of treatment (e.g. elderly and those with chronic disease)  
• Time needed to grow cells ex vivo in sufficient numbers may be excessive |

MSCs, mesenchymal stem cells; EPCs, endothelial progenitor cells.
endothelial dysfunction, a condition characterized by reduced NO bioavailability and a concomitant increase in vascular tone, as well as other phenotypic changes to the corporal smooth muscle. Endothelial dysfunction is believed to be a clinically silent harbinger of impending cardiovascular disease and is notably present in at-risk patients, such as those with hypertension, diabetes, and dyslipidemia.

Because both the incidence of ED and low circulating EPCs are independently correlated to an increased risk of cardiovascular disease, several recent efforts have been made to measure the association between ED and circulating EPC levels. One of the intentions of these studies is to determine whether circulating EPC levels can accurately predict ED and thus serve as a readily available diagnostic biomarker for incipient endothelial dysfunction (see Figure 42.2). In the first study of its kind, Foresta et al. found significantly lower levels of circulating EPCs within those having ED, though not necessarily having known cardiovascular risk factors.

In another study, Baumhâkel et al. showed that circulating EPCs were diminished in patients with both ED and high risk for cardiovascular disease, and decreased EPCs served as an independent predictor of ED.

In a further study, which included ED patients with or without known cardiovascular risk factors, Foresta et al. noted a significant increase in both EPCs and brachial artery flow-mediated dilatation (a clinical measure of endothelial function) after 3 months’ treatment with tadalafil (a PDE-5 inhibitor). The results of this study may be interpreted to suggest a possible link between the restoration of circulating EPCs and improved endothelial function. In a subsequent study, patients with ED and varying intima media thicknesses of the carotid artery were given the oral PDE-5 inhibitor vardenafil in a single 20mg dose. Circulating EPC numbers increased in all test and control groups 4 hours after PDE-5 inhibitor treatment, though those with higher grades of carotid intima media thickness had significantly lower increases in EPCs than the control group.

The authors interpreted these results as suggesting that people with more significant cardiovascular risk factors and endothelial dysfunction may deficiently mobilize EPCs under PDE-5 inhibitor stimulus. Thus diminished EPC mobilization may be a surrogate test for a patient’s capacity for endothelial regeneration and response to PDE-5 inhibitor therapy for the treatment of vasculogenic ED.

Conclusion

Despite the recent evidence demonstrating a reduced number of EPCs in people with ED, it is currently unclear if circulating EPCs will serve as an independent biomarker of ED. One may conclude that low EPCs can be strongly correlated with global endothelial dysfunction of the peripheral vasculature. Recent evidence evaluating circulating EPCs in ED patients may correlate well with penile vascular dysfunction in a select group of patients, although a definitive conclusion that low EPCs are specifically diagnostic or predictive of imminent ED cannot be made at this time. However, there is sufficient evidence to suggest that decreased mobilization of EPCs to PDE-5 inhibitor stimulus portends a poorer response to this form of therapy and may serve as a surrogate marker to determine severity of ED symptomatology. Rather than diagnosing or foretelling ED, the greatest benefit of EPCs may be in their direct therapeutic potential. If EPCs turn out to be a natural reservoir of incipient endothelial cells, then cell-based therapies aimed at delivering EPCs to the dysfunctional corpora cavernosa will be likely to yield significant improvements in erectile response.

Research into stem cell and progenitor cell therapy for ED is currently at an early stage. Nevertheless, the therapeutic success of the pioneering studies suggests that this approach may offer an effective, long-lasting treatment option, or potentially a possible curative treatment regimen for severe ED. The observation that distinct stem cell populations have exhibited milieu-dependent differentiation and functional recovery in models of ED implies that a variety of cell-based approaches may prove efficacious for both vasculogenic and neurogenic-mediated penile vascular dysfunction. However, as we encountered in our early experience with gene therapies for ED, it will take extensive preclinical evidence before any cell-based therapy can be utilized in human clinical trials.

Acknowledgments: This work was funded from a grant from the American Urological Association Foundation and the Astellas Foundation.

REFERENCES


Mechanical, malleable, and soft semi-rigid penile implants for erectile dysfunction

John J Mulcahy

Introduction
Reliable penile implants were first introduced over 35 years ago, in the early 1970s. At the same time the Scott three-piece inflatable model and Small–Carrollon model were introduced. These were soon followed by the Finney Flexirol device and the Jonas malleable device. In the early days of penile implant placement, the semi-rigid rods outsold their inflatable counterparts by a 3:1 margin. Experienced implanters were in short supply and most urologists felt more comfortable inserting the simpler devices with parts contained completely within the erectile bodies. There were problems unique to the inflatable implants such as leaks, cylinder aneurysms, and tubing kinks, which were not seen with the rod-like devices. With time urologists gained experience in placing hydraulic prostheses and successfully managing their associated complications. The manufacturers attended to wear areas by reinforcing or eliminating them and soon the market shifted toward a preference for the inflatable implants, owing to the better quality of erection and the more flaccid resting state that they afforded. In the mid-1980s, American Medical Systems introduced the Hydroflex implant and later the Dynaflex implant and Surgitek Corporation marketed the Flexiflate device. Each of these was composed of paired hydraulic cylinders, one placed in each corporal body. Fluid was transferred between parts of the cylinder by a distal pumping mechanism to give alternating rigidity and flaccidity. Early mechanical failure, patient difficulties in learning the mechanics of inflation–deflation, suboptimal rigidity, spontaneous deflation, and low market share led to the demise of both devices by the late 1990s.

Mechanical penile implants

Omniphase and Duraphase implants
In 1984 Dacomed Corporation introduced the Omniphase prosthesis. This consisted of two rod-like cylinders composed of a series of polysulphone segments that articulated in a ball-and-socket arrangement held together by a central cable attached to a spring. Bending the cylinders would alternately shorten and lengthen the cable, thus allowing the rods to become taut as the segments abutted against each other or flaccid as the segments separated. Cable breakage, difficulty in cylinder selection, and problems with activation–deactivation resulted in a short market life for this device. The intention was to provide a prosthesis that gave the rigidity of the malleable rods but with superior bendability for positioning during intercourse and easy downward positioning without spring back.

The successor to the Omniphase implant was the Duraphase implant. This implant, also sold by Dacomed Corporation, contained the same polysulphone segments without the activation–deactivation switching mechanism. The device was easy to insert, provided reasonably good rigidity, and was easy to conceal without the spring-back seen with the malleable implants. It became a very popular member of the semi-rigid rod category of penile prostheses, but cable breakage and segment wear necessitated replacement of many of these devices sooner than was anticipated.

Dura II prosthesis
The material of the Duraphase implant was changed in an attempt to increase the mechanical reliability. The segments were changed from polysulphone to high-molecular-weight polyethylene, which was five times more durable. The cable was redesigned with smaller and more numerous strands, which in bench testing showed no fatigue after 8 million bends. This improved cylinder was named the Dura II prosthesis (Figure 43.1). It had numerous vendors over the succeeding decade and is now sold by American Medical Systems. The body segments are held together by a cable attached to fixed posts at each end by a spring. A polytetrafluoroethylene sleeve covers the segments, and the entire device is covered by a silicone membrane to prevent adherence to body tissues. There are two diameters available, 10mm and 12mm. Each cylinder in both widths is 13cm long, and proximal and distal tips can be added by attaching these to the body with a set screw. The segments of the body are positioned at the bend angle of the penis. A grid combining glans–pubis distance and total corporal length determines which size proximal and distal tips are to be used to make sure the segments are positioned for optimal bendability. When measuring glans–pubis distance, the distal point should be at the proximal one-third of the glans. The proximal end of the measuring tool should
rest without pressure against the skin of the pubis. In the heavy-set patient, this may be a considerable distance from the pubic bone, but it is the most accurate way of determining the best location of the segments for complete and easy bending of the device. If a discrepancy in intracorporal length between the two sides is observed, the difference in cylinder length should be adjusted by using proximal tips of different sizes or using proximal tips of the longer size and trimming the proximal tip of the cylinder to be inserted on the shorter side. This will ensure symmetric bending of the device. The Dura II cylinders can actually be bent more than the limits of the corporal anatomy will allow.

This is the prosthesis of choice for patients with little or no manual or mental dexterity as it can be positioned upward or downward with the motion of one finger. Patients with a very broad penis will achieve suboptimal axial rigidity during intercourse with the Dura II since there is room laterally for the cylinders to shift. The shortest cylinder implantable is 14cm. The proximal tip can be omitted but the distal tip must be attached. Hence patients with a very short penis or with considerable scarring from removal of a previous implant may not be candidates for this prosthesis. The longest length of this implant if the largest proximal and distal tips are attached is 31cm. A recent report with mean follow-up of 5.7 years showed no mechanical defects in the device placed in 94 patients.*

Malleable implants

Malleable rod implants have a tendency towards spring-back and are difficult to position in a directly dependent position. They also require some manual dexterity to bend up and down as desired. They do, however, give good intrinsic axial rigidity and the newer models have been virtually free of mechanical failure (i.e. wire breakage).

AMS 650 and 600M

American Medical Systems manufactures two variations of a malleable rod implant with a spiral stainless steel wire as the central core surrounded by a solid silicone covering. The AMS 650 basic implant has an 11mm girth and is surrounded by a silicone jacket, which, if left in place, is 13mm in girth. It is provided in 12cm, 16cm, and 20cm lengths, and rear tip extenders can be applied as sizing dictates (Figure 43.2). The AMS 600M is a narrower version with the same basic design with a 9.5mm girth and an outer jacket, which, if left in place, provides an 11.5mm diameter. The lengths supplied are 12cm, 14cm, 16cm and 18cm, and rear tip extenders can be applied as needed in increments of 0.5cm.

Genesis implant

The Genesis, sold by Coloplast, is basically the Accuform malleable prosthesis manufactured by Mentor Corporation to which a hydrophilic coating has been added (Figure 43.3). When the implant is placed in an antibiotic solution, the solution adheres to the implant and is delivered into the wound, where it elutes into the tissues surrounding the implant. Early reports about other implants with this antibiotic coating have shown a significant reduction in the incidence of implant infection. This is the only semi-rigid rod implant with an antibiotic coating. The Genesis comes in 9.5cm, 11cm, and 13mm girths, and each girth size is 22cm in length. The length can be trimmed and a proximal cap added as needed for appropriate sizing to the length of the corporal body. The core of the
cylinder is double-braided silver wire, which is surrounded by silicone.

There are a number of other malleable rod implants that are manufactured and used locally in certain countries. The Jonas prosthesis in Germany and the Silmed prosthesis in Brazil are examples of these.

**Soft semi-rigid implants**

The Small–Carrion and Finney implants that were popular in the 1970s are no longer manufactured. They were composed mostly of silicone and in many cases the support of the erection for vaginal penetration was suboptimal. In addition, the penis was difficult to conceal as it tended to point outward when the patient was standing. Silicone semi-rigid rods are still manufactured and used locally in some countries. The Shah prosthesis in India and the Virilis (Subrini) implant in France (and Italy) are examples of these. The Virilis implant has been used in patients with Peyronie’s disease to help straighten the erection. The patient’s natural tumescence helps give additional girth and support with the silicone rods in the corporal bodies acting as splints.9

**Preoperative preparation**

Patients are encouraged to bathe the genital region with a strong soap for 3 days prior to the procedure. The urine should be sterile, and in the case of patients at high risk for infection, such as those with indwelling catheters or those with neurogenic bladders, prophylactic antibiotics are given for a week beforehand. The skin of the genital area is inspected for sites of infection and these are eliminated before the procedure.

Systemic antibiotics are started after the intravenous line has been placed, before the induction of anesthesia. This will provide tissue levels of the antibiotic while the wound is open during the surgery, and the systemic antibiotics are continued for up to 24 hours afterward. A number of regimens have been recommended. The organisms associated with prosthetic infections are staphylococcal skin contaminants and Gram-negative rods. Although antibiotics are commonly used in conjunction with prosthetic surgery, no study has been performed that demonstrates their effectiveness in preventing intra-operative acquired infections. Many infectious disease specialists recommend against their frequent use because they can promote the development of resistant organisms. In addition the practice is costly and can also lead to the development of allergies to the drugs used. However, frequent irrigation of the wound with an antibiotic solution is a very important feature in reducing wound infections.

The patient’s genital area is shaved and thoroughly prepared with a strong antiseptic solution. If phimosis is present, circumcision should be performed prior to the implant procedure (not simultaneously). The incidence of infection associated with penile implant is low (1–2%). In the event of infection the implant may be removed, the wound thoroughly cleansed with a series of antiseptic solutions, and a new implant inserted (during the same surgery), with success rates in eradicating the infection in the range of 85%.10

**Surgical approach**

A number of incisions have been used for the placement of the semi-rigid rod implants: subcoronal, penoscrotal, infrapubic, dorsal penile, and perineal. The last-named two are seldom used for reasons of cosmesis and difficult access. A very convenient incision to place any semi-rigid cylinder is the ventral penile approach with local anesthesia (Figure 43.4).11

A penile block using lidocaine 1% without epinephrine is placed circumferentially at the base of the penis. A tourniquet is then placed snugly around the base of the penis and 25ml of lidocaine 1% is injected intracorporeally as if performing an artificial erection. Bupivacaine, although longer acting than lidocaine, should not be used intravascularly as it may be cardiotoxic in large doses. After 2 minutes the tourniquet is released, allowing the anesthetic to flow proximally to anesthetize both corporal bodies.

A midline skin incision is made on the proximal half of the ventral penile shaft and carried down to the corpus spongiosum (Figure 43.5). A vein retractor pulls the foreskin at the distal aspect of this incision toward the glans penis. Buck’s fascia and areolar tissue are dissected from the tunica albuginea about two-thirds of the way down the shaft of the penis. Two stay sutures are placed on each side of the corpus spongiosum at this location. These will be used to hold open the corporotomy and as reference points for corporal measurements. A 3cm incision is made between the stay sutures, and the plane of dissection is developed under the tunica distally to the subglandular area and proximally to the ischial tuberosities using Metzenbaum scissors. Dilators starting at size 8 or 9 are passed in each direction.

![Figure 43.4 Ventral penile incision for placing semi-rigid rod implants.](image-url)
All semi-rigid cylinders come in two or more fixed width sizes, and the question arises as to which size to use. The decision should be made before opening the sterile package containing the device and possibly contaminating two sets if the first one is not the right size. To determine which size of two would be a better fit, place two dilators of the smaller size simultaneously side by side into the corporal bodies, first proximally and then distally. The surgeon’s thumb should then be apposed to his or her index finger on the shaft of the penis between the two dilators (Figure 43.6). Slight separation of the dilators between the fingers would indicate an ideal fit of that width cylinder. If no separation is found, a snug fit with that size cylinder would result. If the thumb can easily touch the index finger between the dilators, a relatively loose fit will be achieved with that size of paired rods. The corporal cavities should be dilated one size wider than the cylinder width to be inserted to allow easy passage of the device in both directions.

The corporal length is then measured in both directions with a stay suture used as a reference point, and the two dimensions added to give the total corporal length. For all of the semi-rigid rods, inserting a rod length about 0.5 cm shorter than the total corporal length will give better bendability and less discomfort. If cylinders are too long, an ‘S’ configuration or snake-like appearance, with spring-back during ventral bending, will be noted.

Once the appropriate length and width have been determined the cylinders are removed from the sterile package and appropriate tips or extenders are applied. The cylinder is inserted proximally to the ischial tuberosities. A vein retractor is then used to pull the distal end of the corporotomy over the exposed end of the rod (Figure 43.7). The rigid cylinders need not be bent using this technique. The wound is then closed in three layers: corporotomy, subcutaneous tissues, and skin. The advantages of this incision include preservation of the foreskin in the uncircumcised patient, and the avoidance of overlapping suture lines.

**Postoperative care**

The patient is discharged from the recovery room on the day of surgery or from the hospital the following day. Antibiotics are continued for 24 hours until the wound is sealed. Catheters or drains are left in place at the discretion of the surgeon. The penis is usually kept pointing upward or positioned in the crease of the leg to avoid friction of the head against the undergarments. Use of the penis for intercourse is usually resumed 5–6 weeks after implantation.

**Reliability and troubleshooting**

The durability of the Dura II implant has been superior to that of its precursor, the Duraphase, with no mechanical failure reported in 85 patients at a mean follow up of 5.7 years. If segment wear were to occur, little or no tension would remain on the springs attached to the fixed posts, the segments would become loose, the rods would lose their rigidity, and the penis would appear floppy. Wire breakage of the malleable rods is very unusual, but cases have been reported. If these mechanical problems occur, the cylinders can easily be replaced by a surgical approach similar to that used for their insertion. The ventral penile approach using a penile block on an outpatient basis is commonly used.
Special considerations

Erectile dysfunction (ED) is a common sequel of spinal cord injury and other neurologic diseases. Penile implants have been used successfully to restore erectile ability in these conditions. In a study of 245 neurologically impaired patients in whom a variety of penile implants was placed, the distal erosion rate for semi-rigid rod prostheses was 18%, while the erosion rate with hydraulic implants was much lower. The need for catheter placement in this group with an always-firm implant next to the fossa navicularis could contribute to a pressure-associated erosion. This group also has diminished sensitivity in the penis and might not appreciate the friction and accompanying pain as the firm implant and penis continually rub against the undergarments. A hydraulic prosthesis is recommended for patients in this category and, if they are manually impaired, the partner should be instructed in the operation of the pump.

If a proximal perforation of the corporal body occurs during placement of a semi-rigid rod implant, the area must be secured to prevent proximal migration of the rod in the postoperative period. A ramrod effect will occur, and as the cylinder moves back and forth it will broaden the perforated area and soon be palpable in the buttocks. A suture sling placed as the rod is inserted into the corporal body will solve this problem. A 3–0 prolene suture with double swedged-on needle is placed through the proximal tip of the cylinder or through the rear tip extender. The cylinder is then positioned in the corporal body and each needle at the end of the suture is brought through the tunica albuginea at the midpoint of the corporotomy. The corporotomy is closed and the suture of the sling is tied snugly over the corporotomy. If the rod needs to be removed in the future, the suture is cut as the corporotomy is re-opened and the prolene suture is easily pulled out of the wound. If a proximal perforation occurs during placement of a hydraulic cylinder, the input tube will act as a buttress to prevent proximal migration if it exits the corporotomy as it comes off the cylinder.

Satisfaction

Penile implants have seen consistent improvement in the numbers placed in recent years following the precipitous decline in numbers with the arrival of the phosphodiesterase type 5 inhibitors in 1998. About 20,000 are being placed annually worldwide, with about 80% of these being in the USA.

There the ratio is about 95% hydraulic implants and 5% malleable or mechanical implants. In the rest of the world the ratio is closer to 50% rods and 50% inflatable implants, owing to cost considerations. Kearse et al., in a multicenter evaluation of the Dura II prosthesis up to 2 years after implantation, noted no mechanical failures and patient satisfaction rates in the range of 80%. Fallon and Ghanem found overall satisfaction of about 90% in a series of 142 patients with either an inflatable or malleable implant. Eighteen percent of the rod group and 6% of those with an inflatable device believed that they had chosen the wrong prosthesis. Twenty-six percent thought that their prosthesis did not meet expectations in that it was too short or not stiff enough. Eighty percent of patients were happy with the results. Krauss et al. completed a prospective study of 19 malleable implant recipients and their partners and found that 85% of patients and 70% of partners were pleased with the function of the device. A total of 92% of patients and 90% of partners indicated that they would choose the implant surgery if faced with the same option again. The size of the penis postoperatively was a major disappointment to many patients, although with time and acclimatization to the new device this became less of a concern. In a previously cited long-term study of the Dura II implant, 76% reported satisfactory rigidity and 87% reported satisfactory ease of concealing the device. Eighty-seven percent of patients reported that the prosthesis improved their quality of life, 85% would undergo the implant surgery again, and 88% would recommend the Dura II prosthesis to a friend. In a study from the Middle East of 50 patients with an AMS 650 or Mentor Accuform malleable implant, 70% of patients and 57% of partners were satisfied with the prosthesis. Dislike for the device was the most common reason for dissatisfaction of patients with the device, while a sense of unnaturalness was the reason for the partners.

Conclusion

Mechanical, malleable, and soft semi-rigid penile implants continue to play a significant role in the management of ED. Ease of insertion, low malfunction rate, lower cost, and simplicity of the operation have made them a popular choice in many circumstances. Satisfaction rates in the range of 70–80% are consistently higher than those of other less invasive treatments. The predictable and reliable results which these devices afford add to the patient’s confidence in his ability to perform sexually. His overall outlook on life, productivity, and body image are consequently enhanced.

REFERENCES


Introduction

The concept of implanting a penile prosthesis for the management of erectile dysfunction (ED) is based on a natural anatomical component found in several species (e.g., dogs), the os penis or baculum, which supports and maintains the penis in erection. For men who are non-responders to oral ED treatment, in whom vacuum erection devices have failed, or who have contraindications for using intracavernosal or intraurethral pharmacotherapy, insertion of a penile prosthesis remains a very satisfactory and effective treatment alternative.

An ideal penile prosthesis should create a normal-looking penis in its erectile and flaccid state. The nearest to this ideal is the inflatable penile prosthesis (IPP), which was developed to mimic the natural hydraulic event of the erection (therefore providing a more natural erection and detumescence). These prostheses are composed of two inflatable cylinders, a reservoir, and a pump mechanism. When an erection is desired, the pump is activated and fluid (saline) is transferred from the reservoir into the cylinders. By activating the deflation valve, detumescence is induced. Current IPPs come in self-contained or in multi-component (two-piece or three-piece) configurations.

Self-contained inflatable penile prosthesis

Dynaflex (American Medical Systems) is a self-contained penile prosthesis that is made of two individual cylindrical elements, each one containing the operating elements for activation and deactivation (Figure 44.1a). The reservoir is at the rear end of each cylinder, the mid-part of the cylinder contains the inflatable chamber, and the distal end of the prosthesis has the pump (at the level of the glans penis). When each pump is activated, 2–4 ml of saline is added to the inflation chamber and rigidity is achieved (see Figure 44.1b). Deflation is carried out by bending the penile shaft 55° or more. This activates the deflation valve and returns part of the liquid to the reservoir (see Figure 44.1c). This prosthesis is a compromise between the semi-rigid prostheses and the multi-component devices.

Its advantages include the fact that it has no tubing or external components; in addition, the implant procedure is easy. However, there are difficulties associated with activating two separate distal pumps; it provides less rigidity than the semi-rigid or multi-component devices; occasional buckling and deflation has been experienced during intercourse; and it has less flaccidity (when deflated) than the multi-component devices. Furthermore, it is limited to the small-to-average-sized penis because of the inadequate rigidity in large or long penile sizes.

Two-component inflatable prostheses

The two-component inflatable penile prostheses, Ambicor (American Medical Systems) and Mark II (Mentor) (Figure 44.2), have a pair of erectile cylinders and a pump in the scrotum that acts as a reservoir, holding 15–20 ml of liquid (Figure 44.3). These prostheses are mostly used in patients in whom an abdominal reservoir cannot be implanted. They are activated by squeezing the pump and deactivated by simultaneously squeezing the pump and bending the penis. They are simple to inflate and deflate. However, they cannot enhance penile girth and their flaccidity is less than the three-component prostheses because of fluid remaining in the cylinders. In large penises, the rigidity that they create is restricted because of the limited volume of fluid contained in the reservoir.

Three-component inflatable prostheses

The three-component prostheses, Ultrex, CX, and CXN (American Medical Systems) and Alpha–1 Titan (Mentor) have two erectile cylinders, a reservoir at the Retzius space and a small pump in the scrotum which transfers the liquid from the reservoir to the cylinders and back (Figures 44.4 and 44.5). These prostheses produce the most natural-appearing erection. Because of the large amount of liquid held in the reservoir they create a good rigidity even in large penile sizes. Upon deflation, good flaccidity is achieved since the liquid in the cylinders is completely returned to the reservoir.
not only for reaching an accurate diagnosis, but also for medicolegal reasons. The preoperative evaluation is covered in Chapter 45.

In addition to the pre-operative evaluation, when the decision for a penile prosthesis implantation is being made, it is recommended that all available prosthesis options are presented to the patient and the partner, including costs and the risk–benefit profile of each type of implant: have the patient or the couple as decision-making partners.

As with every mechanical device the penile prostheses also have their ‘wearing-out’ time and mechanical dysfunctions,
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which may necessitate a surgical repair.\textsuperscript{1,2} These issues should be discussed and documented in order to prevent future medicolegal problems.

\textbf{Pre-operative preparation}

Prevention of infection is the most important part of this surgery.\textsuperscript{3} This can be achieved by proper preoperative preparation of the patient; the use of intra-operative, wide-spectrum systemic antibiotics and intra-operative local antibiotic irrigations; and pre- and postoperative wide-spectrum antibiotic coverage.

These preparations are performed in a step-wise fashion starting with the patient taking a shower with an antiseptic soap (e.g. Betadine) the evening before and on the morning of surgery (to decrease the bacterial colony count on the skin); parenteral administration of cefazolin 1g and gentamicin 160 mg 30–60 minutes before surgery. After the patient has been anesthetized and positioned on the operating table, the genitalia are shaved (using hair clippers). The genitalia, thighs, inguinal folds and abdomen are then cleaned with iodine scrub for 10–15 minutes prior to the same area being painted

\textbf{Figure 44.3} The pump of the two-component prosthesis acts also as the reservoir of the liquid to inflate the cylinders.

\textbf{Figure 44.4} Three-component inflatable penile prostheses: (a) Ultrex and (b) Titan.

\textbf{Figure 44.5} (a) Placement of the three-component prosthesis. (b) X-ray view of the contrast-filled three-component prosthesis in erect shape. Note the collapsed reservoir. Contrast solutions are not used any more for filling the inflatable prostheses.
with non-alcoholic iodine solution. The patient is then draped. Members of the team who scrubbed and draped the patient change their gloves and wash away residual powder from the new gloves with saline.

**Surgical approach to the corpora cavernosa and dilatation of the corpora cavernosa**

The penoscrotal approach is the ideal ventral corporeal approach for the implantation of self-contained or multi-component penile prostheses. It also provides an excellent approach to the dorsal side of the corpora cavernosa for incising Peyronie’s disease plaques when this procedure is combined with prosthesis implantation. The steps involved in the implantation of an IPP are shown in Figure 44.6.

A 5–6cm long midline skin incision is made. Through this incision, at the level of the penoscrotal angle, the corpus spongiosum and corpora cavernosa are identified and prepared. A pair of parallel stay sutures are applied to the tunica albuginea of each corpora to allow their opening for dilatation of the cavernous tissues with Hegar type dilators. If a sepal perforation occurs during dilatation, the direction of the dilatation is diverted laterally to enter the proper corporeal space. In the event of urethral perforation, some surgeons prefer to stop the procedure and drain the bladder either with a small-caliber urethral catheter or suprapubically. If during dilatation, difficulty in inserting the large-caliber dilators is felt, the use of long blunt-tipped scissors can be helpful for increasing the dilatation. The scissors are inserted closed into the corpus and the blades are gently opened in the 12 o’clock and 6 o’clock position for performing the dilatation. Care should be taken not to open the blades toward the septum or the urethra since this may cause perforation. As with the semi-rigid prosthesis implantation, if one of the cavernous bodies is severely fibrosed, it is recommended that one cylinder be implanted in the contralateral corpus and that the fibrotic corpus be abandoned. Inadequate dilatation of the corpora can cause unnatural-looking erections, especially when an inflatable prosthesis is used. Dilatation not reaching the tip of the corpora can cause insertion of a shorter cylinder than needed, resulting in ‘drooping glans’ or penile asymmetry.

Dilatation of the proximal corpora also should be done carefully to prevent perforation of the crura. Perforation of the crus can cause early backward migration of the cylinder. When a curial tear occurs, there is a need to perform a ‘wind-sock’ repair using a Goretex or Dacron vascular graft, closed at one end. This ‘wind-sock’ is inserted toward the torn crus and fixed to the tunica albuginea with non-absorbable fine sutures. Then the proximal end of the cylinder is inserted into the ‘wind-sock’. An alternative is to insert the rear part of the cylinder into the ‘wind-sock’ and then insert them together into the proximal corpus and fix the graft to the tunica albuginea at the proximal level of the corporotomy incision (Figure 44.7).

From the incision stage of the procedure, and throughout the entire procedure, the open tissues should be frequently irrigated with an antibiotic solution (e.g. gentamicin 160 mg diluted in 500 ml of saline).

**Handling the prosthesis**

After completing the dilatation, the length of each corpus is measured separately with the measuring device and the proper length prosthesis is chosen. After removing the inflatable prosthesis from its packing tray, all of the components are visually inspected and the air suctioned out. The cylinders, reservoir, and pump are checked for integrity by filling them with isotonic saline solution and removing it several times.

It is recommended that all the components of the prosthesis be kept immersed in an antibiotic solution (e.g. gentamicin 160 mg in 500 ml of saline) from the time of removal from the packaging until implantation.

**Insertion of inflatable prostheses**

After dilating the corpora, the tip of the inflatable cylinder is attached to a Furlow or Keith inserter with a suture. Then the inserter is advanced from the corporotomy incision toward the glans. When the tip of the inserter reaches the tip of the corpus, its needle is advanced to pass through the glans and the inserter is removed. By pulling the suture, the tip of the cylinder is pulled until it sits snugly at the tip of the distal corpus. Then the proximal end of the cylinder is manually placed through the corporotomy incision toward the crus. When necessary, rear tip extenders are used to add length to the cylinders to fit them to the length of the corpora (Figure 44.8). When the cylinder sits satisfactorily in the corpus the suture at its tip is removed. The same maneuvers are repeated for inserting the second cylinder.

It is recommended that the pump and the reservoir be implanted according the manual preference of the patient. In left-handed patients they are implanted at the left scrotum (with the reservoir to the left side of the Retzius space) to allow its easy manipulation. To allow easy access to the patient, the pump is inserted in a sub-dartos pouch created at the anterior face of the scrotum. The abdominal reservoir is inserted into the Retzius space through a tunnel created through the transversalis fascia at the level of the external inguinal ring. Proper insertion of the reservoir into the Retzius space is important for reducing the risk of spontaneous inflation of the cylinders. After it has been positioned, the reservoir is filled with 60–100 ml of saline and its tube clamped.

After the pump has been implanted, the tubes from the cylinders and the reservoir are trimmed to length and connected to the pump. Before the incision is closed, the functioning of all the components of the prosthesis are tested by inflating and deflecting the cylinders, and leaks at the connections are checked.

**Inflatable penile prosthesis implantation for the repair of Peyronie’s disease curvature**

Only about 10% of the Peyronie’s disease curvatures need to be surgically corrected.4 Surgical intervention is required when coital function is impaired. Surgical procedures for the
Figure 44.6 Steps for implanting an inflatable penile prosthesis. (a) Penoscrotal incision. (b) Preparation of the corpora cavernosa. (c) After its dilatation the length of the corpus cavernosum is measured. (d) The suture to help pull the inflatable cylinder into the corpus cavernosum is passed through the tip of the cylinder. (e) The pulling suture is thread through the Furlow or Keith inserter to attach the tip of the cylinder to the inserter. With its needle retracted, the inserter will be advanced toward the glans. (f) When the tip of the inserter reaches the tip of the corpus cavernosum, the needle is pushed forward to pass through the glans. (g,h) The inserter is removed and the proximal end of the cylinder is inserted toward the crura.
Figure 44.6 (Continued)  (i,j) The distal part of the cylinder is inserted into the distal corpus cavernosum and the distal cylinder is pulled toward the glans by pulling the suture. (k) The incision of the tunica albuginea is closed using absorbable sutures. (l) The implantation site for the scrotal pump is prepared in the scrotum. (m, n) The implantation site for the reservoir is prepared at Retzius space by blunt finger dissection and the use of a blunt dissector. (o) All the tubing between the cylinders and the pump is connected, and the pump is connected to the reservoir. (p) At the end of the procedure, the pump is activated to inflate the cylinders.
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Figure 44.7 (a) A crural tear and (b) the use of a ‘wind-sock’ to repair the tear.

repair of Peyronie’s disease are divided into three major groups:

- plaque surgery (incision or excision of the plaque and grafting or incision through the plaque);
- corporoplasty; and
- penile prosthesis implant with or without plaque manipulations (i.e. without incisions or corporoplasty).

Patients with calcified plaques invading the cavernous tissues and with impaired erectile capacity who do not respond to pharmacotherapy are the best candidates for penile prosthesis implantation. Penile prosthesis implantation alone or combined with corporeal reshaping is needed when penile angulation is severe.\textsuperscript{5-13}

The use of semi-rigid penile prosthesis implants for the correction of penile deformations caused by Peyronie’s plaques was proposed almost 30 years ago. This was almost immediately followed by the use of IPPs to restore erection and straighten the penis in Peyronie’s disease.\textsuperscript{14,15} The effect of penile prosthesis implantation in Peyronie’s disease patients is double: by splinting the curved corpora the deformity is straightened, and by restoring erection and providing a straight penis comfortable penetration becomes possible.

In these patients, after implanting the prosthesis the cylinders are inflated to observe the degree of straightening achieved. In mild residual curvature the penis can be manually straightened. In order to achieve a good straightening in a severely deformed penis it is recommended to add plaque incisions to the inflatable prosthesis implantation. Single or multiple transverse incisions can be performed using electrocautery (cutting current), with the prosthesis \textit{in situ} (cutting current incises tissue but cannot cut silicone rubber) (Figure 44.9). These transverse incisions can be left open.

The surgical wound is irrigated again with an antibiotic solution and closed in two layers using fine absorbable sutures.
A non-compressing dressing is applied. At the end of the procedure the prosthesis is left in a semi-inflated–semi-rigid state.

**Postoperative period**

It is best to do the procedure with a short hospitalization period or as day-care in order to reduce the risk of hospital-acquired infections. The patient is prescribed oral wide-spectrum antibiotics for a period of 2 weeks. Since almost all patients have pain after penile prosthesis implantation, oral analgesics or even oral narcotics are prescribed for the painful period. The initial painful period of 2–3 weeks turns into soreness, which may continue for a further 2–3 weeks. Driving is not allowed for 2–3 weeks.

Sexual activity can be resumed no sooner than 6 weeks after implantation, and only if there is no pain. In the case of continuing pain or severe soreness, sexual activity is delayed for another 2–4 weeks. At this stage the patient is instructed how to activate and deactivate the prosthesis. The patient’s partner also is trained how to operate the penile prosthesis in order to create co-operation between the partners and to decrease partner’s rejection of the procedure. This also helps in cases in which the patient lacks the manual dexterity for activating the prosthesis.

Complications of penile prosthesis implantation and their management are discussed in Chapter 45.

**REFERENCES**


Introduction

Although the problem of erectile dysfunction (ED) has been recognized since ancient times, adequate treatment has been available only since the second half of the 20th century. In the early 20th century, attempts to design surgical procedures to provide rigidity of the penis for sexual activity and to recreate the os penis of lower animals was unsuccessfully attempted by a variety of surgeons. The first attempts at penile prosthesis implantation were in the 1930s, when Bogaras described the use of a tailored section of rib cartilage to produce penile rigidity, in a fashion similar to that provided by the os penis of walruses, squirrels, and other animals. These tailored grafts, however, were unsatisfactory, and cartilage reabsorption, infection, extrusion, and progressive angulation resulted in abandonment of this procedure. Bergman et al., in 1948, reported the use of a rib graft with similar complications.

Development of newer synthetic materials in the 1950s and 1960s propelled the advancement of prosthetic devices in the treatment of a variety of medical conditions, including ED. Early reports by Goodwin et al. in 1952 suggested that synthetic materials could produce satisfactory results when implanted into the penis for ED. The era of modern penile prosthetic devices began with the development of silicone-based prosthetic materials in the late 1960s as a result of the space program. In 1968, Lash et al. reported on 28 patients using single silicone prosthetic devices with good results, and in 1972 Pearman designed a single silicone silastic prosthetic rod placed beneath Buck’s fascia in 126 patients (Figure 45.1). Although these devices increased the success of penile prosthesis implantation, their placement beneath Buck’s fascia provided little stability, significant discomfort, and a non-physiological penile shape. Extrusion rates were also high with these initial attempts at penile prosthesis design.

Types of penile prostheses

Modern penile prosthetic devices were first developed in the early 1970s, when Scott et al., together with Small et al., reported the implantation of penile prosthetic devices into the corpora cavernosa to fill the corpora cavernosa and to provide a physiologically functional erection with good cosmetic results. The development of semi-rigid rod prostheses for which the Small–Carriion device is a prototype, has been previously described (see Chapter 43). Scott et al., in 1973, described the second group of penile implants, which are inflatable. These devices have undergone multiple revisions and new designs between the early prosthetic devices and the currently available inflatable penile prostheses. The initial device consisted of four components, including an inflation pump, deflation pump, reservoir, and two implantable cylinders. The current device has combined the inflation and deflation pump into a single pump.

There are currently two varieties of hydraulically inflatable penile prostheses, including two-piece and three-piece inflatable penile prostheses. Early three-piece inflatable penile prostheses were widely used, with excellent erections and a physiologically flaccid–appearing penis between uses. Mechanical malfunction rates in these early devices, however, were reported in excess of 60% of cases.

Current inflatable prosthesis devices, however, have a greatly improved mechanical reliability. These current devices (Table 45.1) are multiple-component inflatable penile prostheses, of which two- and three-piece models are available. There were single-rod inflatable penile prostheses, which have been termed the ‘hydraulic hinge’ penile prostheses. Because these latter prostheses did not provide a significant increase in penile girth and are frequently limited in flaccidity, and because their reliability was poor, these devices have been removed from the market.

Current penile implants

Two three-piece inflatable penile prostheses are currently available from American Medical Systems (Minnetonka, MN, USA) as the AMS 700 CX InhibiZone and the LGX (formerly Ultrex) InhibiZone prostheses, and the Titan prosthesis is available from Coloplast (Minneapolis, MN, USA) (Figure 45.2). The AMS cylinders are available as 700 CX, 700 CXR, and 700 LGX. The cylinder design consists of a three-layer construction, with an inner layer of silicone, middle layer of limited-expansion woven Dacron mesh in the CX cylinders and middle layer of woven Dacron–Lycra in the LGX cylinders, with an outer layer of silicone to prevent tissue adherence from the middle-layer mesh. Whereas the CX cylinders have controlled expansion capabilities, the LGX cylinders permit girth expansion to 18mm and elongation by as much as 20% in length to allow increased filling of the corporal bodies and possible axial expansion. A paralyne coating has been added between the three layers to diminish the fabric separation and ultimately decrease cylinder aneurysm.
The prosthetic cylinders of the Coloplast Titan and Alpha-1 prostheses are constructed of Bioflex material that expands to 20 mm in girth without axial elongation. As a result of its single-layer design, more rigid wall, and resilient construction, the Bioflex material appears to be more durable than single-layer silicone, although the currently available triple-layer silicone prostheses appear to have durability equivalent to that of Bioflex cylinders. Aneurysmal dilatation is rare with both of these cylinder designs but has been reported. Similarly, other design changes over the past 20 years, including replacement of stainless steel connectors with plastic connectors, addition of non-kinked tubing, single-design construction, Teflon cylinder input sleeves, and multiple-layer cylinders, have improved the longevity of these devices. Because the cylinder portion of the inflatable system functions at significantly higher pressure than the reservoir portion, most complications occur where pressure maintenance is important. Therefore, strengthening or eliminating connectors, strengthening cylinder materials, and input tubes has decreased mechanical malfunction rates from more than 30% to less than 5%. Estimated life of these implants is 12–15 years, which is longer than for almost any other human implanted prosthesis.

Subsequent to investigations that identified the efficacy of coating prostheses with a combination of rifampin and minocycline to inhibit bacterial growth, American Medical Systems developed a new penile prosthesis coating that received approval in the USA from the Food and Drug Administration in May, 2001. In the InhibiZone™ prosthesis, tissue-contacting surfaces are impregnated with quantifiable doses of rifampin and minocycline that elute into the area surrounding the prosthesis post-operatively. Both drugs elute initially at high rates, with a significant drop-off in rifampin after day 1 and in minocycline by day 7. The Coloplast Corporation has developed a coating called Resist and applied it to their Titan inflatable penile prostheses. This concept is that a hydrophilic coating on the Bioflex surface will decrease bacterial adherence that precedes biofilm formation. Further, the coating will absorb antibiotics of the surgeon’s choice and permit these to elute from the implant for 1–3 days after implantation to decrease bacterial adherence. This concept has been evaluated in vitro and has promise for reducing infections. A large multicenter trial has confirmed the reduction in prosthesis-associated infections with the Resist coating.

The three-piece inflatable penile prostheses continue to be the most satisfactory prostheses while they remain functional.

**Table 45.1 Currently available penile prostheses**

<table>
<thead>
<tr>
<th>Semi-rigid rods</th>
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<tr>
<td>Malleable (Coloplast)</td>
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<td><strong>Inflatable</strong></td>
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<tr>
<td>700 CX Inhibizone (AMS)</td>
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<td>700 LGX Inhibizone (AMS)</td>
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<td>Titan (Coloplast)</td>
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<td>Ambicor (AMS)</td>
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<tr>
<td><strong>Mechanical</strong></td>
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<tr>
<td>Durall (AMS)</td>
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AMS, American Medical Systems

**Figure 45.1** Pearman penile prosthesis placed beneath Buck’s fascia through dorsal penile incision.

**Figure 45.2** Multiple-component inflatable penile prostheses. (a) AMS 700 LGX Plus penile prosthesis. (Courtesy of American Medical Systems, Minnetonka, MN, USA. Illustration by Michael Schenk.) (b) Alpha-1 penile prosthesis. (Courtesy of Coloplast Corporation, Minneapolis, MN, USA.)
These prosthetic devices produce the most natural-appearing erection in girth and length, and impart satisfactory rigidity and excellent flaccidity for optimal concealment. They also have advantages for many patients with complex penile implantations, since the flaccid position removes pressure from the corpora cavernosa and decreases the possibility of erosion in these highly difficult implantations. Pressure within the corpus cavernosum is reflected upon the layers of the tunica albuginea. The thinnest portion of the tunica albuginea appears to be the ventral aspect, which lacks longitudinally directed outer bundles of collagen and corresponds to the area of most common penile prosthesis extrusion.25 In difficult situations, such as in patients who have had previous extrusion or infection, in patients with severe diabetes or peripheral neuropathy, or in patients with severe corpus cavernosum fibrosis or reconstruction, the inflatable penile prosthesis may be the optimum choice.24,26,27 To improve ease of surgical implantation and to remove a portion of the prosthesis placed within the abdominal region, two-piece prostheses were designed (Figure 45.3).

Currently available is the AMS Ambicor prosthesis. The previously available Uniflate 1000 (Surgitech) is still encountered in patients implanted with these devices in the early 1990s.28 Because the Ambicor two-piece inflatable prosthesis eliminates the separate reservoir, additional fluid is available by a combination of proximal cylinder and pump reservoir. Although these devices provide adequate erection in many patients, the limited reservoir capacity decreases flaccidity and may, in some patients, diminish rigidity.29 These prostheses are especially difficult to deflate in patients with small penises and frequently provide inadequate rigidity for patients with longer penises. In these devices, instead of cycling to full inflation, 15–20ml of fluid is transferred and at least 5–10ml of fluid remains within the cylinders between uses. This difference in cycled volume may decrease flaccidity and be objectionable to some patients. Although they are less optimal than three-piece devices, these two-piece implants may be ideal for patients in whom reservoir placement is difficult or contraindicated. Such patients as renal transplant recipients and those who have undergone significant radical pelvic exenteration procedures, as well as patients with surgically implanted vascular prostheses, may benefit from two-piece devices.

Patient selection

Although there are a variety of penile prosthesis designs currently available for implantation, not all patients with ED are candidates for penile prosthesis implantation. Careful counseling of patients before penile implant procedures avoids many of the problems with postoperative dissatisfaction. Despite careful counseling, however, many patients enter penile prosthesis procedures with expectations that cannot be met by penile prosthesis surgery. Complaints about decreased penile length compared with the pre-implant state, decreased penile sensation, and ‘coolness’ of the penis and glans penis, as well as chronic pain and partner dissatisfaction, are among those that patients may voice despite adequate surgical implantation and satisfactory mechanical functioning. Fortunately, these complaints are unusual and more than 90% of patients report satisfaction with their prostheses.15,28 Many patients who are dissatisfied with their penile prostheses will benefit from sexual counseling or continued counseling assistance from the implanting surgeon to be sure that they are able to operate the device satisfactorily and understand its use.29

Most patients’ dissatisfaction results from difficulty with functioning and unrealistic expectations.15 Discussions with patients should include the concept that penile prostheses do not create normal erections but only support the penis for sexual activity. Penile prosthesis surgery brings about the ability to resume sexual functioning and vaginal penetration, but decreased penile sensation, length, and engorgement may result in some patients. Furthermore, patients should be made aware of the possibility of mechanical malfunction, infection, and other common complications that may compromise the results of their penile implant. Patients should also be advised that a penile prosthesis will not improve libido or ejaculation. Patients frequently report delayed or difficult ejaculation initially following penile prosthesis surgery. This delay is primarily a result of inadequate preparation, stimulation and psychological adjustment to the prosthesis. Most patients require 3–6 months of prosthesis use, with careful attention to perpetual stimulation, before ejaculation routinely returns to preoperative levels.24,30 Mulhall et al. used the standardized instruments – the International Index of Erectile Function (IIEF) and the Erectile Dysfunction Inventory of Treatment Satisfaction (EDITs) questionnaires – to evaluate the results of penile implants.30 They showed a slow increase in these indices but excellent function at 6–12 months. Because the prosthesis neither improves nor detracts from preoperative ejaculatory ability, patients must be counseled regarding their preoperative ejaculatory ability before a prosthesis placement.

Once the discussion and demonstration of penile implant varieties has been carried out, patients can be counseled about the most appropriate penile prosthesis for their individual use. Patients may choose a specific prosthetic type based on

![Figure 45.3 Two-piece Ambicor inflatable penile prosthesis. (Courtesy of American Medical Systems, Inc., Minnetonka, MN, USA. Illustration by Michael Schenk.)](image-url)
their needs and preferences. Younger patients with normal manual dexterity often choose a three-piece inflatable penile prosthesis because appearance in the flaccid position is important, particularly for patients who wear stylish, form-fitting, athletic clothing or who shower in public at a health club or other athletic facility. For these patients, implantation of a semi-rigid rod penile prosthesis requires a significant lifestyle change and they are better served with an inflatable-type prosthesis. Similarly, patients with Peyronie’s disease, secondary implantation, or significant peripheral neuropathy (such as occurs in severe diabetes) are best served with an inflatable penile prosthesis because interior tissue pressures are diminished between uses and the possibility of extrusion is diminished.\textsuperscript{30,32} For patients in whom the convenience of inflation and deflation are not important, the risks of mechanical malfunctions may outweigh the disadvantage of a malleable penile prosthesis. Such patients as paraplegics who require an external urinary collection device, those with inadequate manual dexterity, or those with significant obesity may be better served with a malleable or mechanical penile prosthesis. Device cost may be a concern for patients without insurance coverage, and these patients may choose a less costly malleable implant.

**Surgical implantation of penile prostheses**

Surgical implantation of penile prostheses can be carried out using a variety of surgical approaches and incisions. Multipiece prostheses can be implanted by the infrapubic or penoscrotal approaches. Although individual surgeons have a variety of rationales for their choice of approach, there does not appear to be any clear advantage in patient satisfaction or outcome of either of the two approaches.\textsuperscript{35,36} Previous abdominal surgical procedures, in whom reservoir placement is difficult, may be better served with an infrapubic approach, whereas patients with massive obesity may be better approached through a penoscrotal incision. Two-piece devices (because no separate reservoir is present) are best implanted through a penoscrotal incision. The infrapubic approach is usually carried out with a horizontal incision approximately one finger-breadth above the symphysis pubis, allowing implantation with an easily concealed incision once the pubic hair regrows (Figure 45.4). In patients with significant obesity or a previous midline incision, however, a midline incision carried out to the base of the penis facilitates exposure of the corpus cavernosum and improves the ability for corpus cavernosum dilatation. Because the penoscrotal approach requires differentiation of the corpora cavernosa from the corpus spongiosum during resection, initial placement of a Foley catheter is preferred.

The infrapubic approach allows more direct dissection of the corpora cavernosa; however, because of the dorsal neurovascular bundle, injury is possible, resulting in decreased distal penile sensation in some patients. The choice of surgical approach does not appear to have an impact on infection rates. Carson et al. reviewed more than 700 patients with primary penile implants and demonstrated no difference in infection with scrotal or infrapubic surgical approach.\textsuperscript{11}

**Infrapubic approach**

Surgical implantation of a multipiece inflatable penile prosthesis is by the infrapubic approach (see Figure 45.4), which begins with a (usually) horizontal incision one finger-breadth above the pubic symphysis. In obese patients, however, a midline incision may facilitate dilatation by improving exposure of the corpora cavernosa. Similarly, if a patient has a previously healed midline incision, this incision can again be used for the infrapubic approach to penile prosthesis implantation. After incision of the subcutaneous tissue, the section is continued to the rectus fascia. The rectus fascia is incised horizontally and dissected cephalad for approximately 2–3cm. A midline separation of the rectus muscles is carried out and, with sharp and blunt dissection, a pouch is created beneath the rectus muscles to insert the inflatable reservoir comfortably without compression. This step is eliminated by the use of a two-piece penile prosthesis.

The dissection is then carried out over the corpora cavernosa. Sharp and blunt dissection is begun on either side of the pubic symphysis; identifying the dorsal neurovascular bundle. It should be noted that the dorsal nerves of the penis lie approximately 2–3mm lateral to the deep dorsal vein. Once Buck’s fascia has been dissected free from the tunica albuginea, the shiny white tunica albuginea is fixed with two parallel traction sutures.

A corporotomy incision is then carried out between the traction sutures and the corpora cavernosa entered. The corporotomy incision can be carried out with scalpel or electrocautery. Metzenbaum scissors are then used carefully to initiate the tunnelling of the corpora cavernosa, gently spreading the cavernosal tissue both proximally and distally until the ischiolabial tuberosities and crura are encountered, and distally palpating the glans penis to identify the most distal aspect of dilatation. Hagar dilators can be used (size 9–14F), or Brooks or Pratt dilators can be used (Figure 45.5). If fibrosis is encountered, Rosillo cavernotomes can be used to dilate and lyse fibrosis to size 12. Once dilatation has been adequately
carried out bilaterally, the Furlow insertion tool is introduced or is used to measure the length of the corpora cavernosa, using a traction suture as a central point of reference. The proximal and distal measurements are added together to identify total corporal length and obtain appropriate-sized inflatable cylinders. A length slightly less than this measurement is usually selected to permit comfortable positioning of the cylinders. Rear tip extenders of size 1cm, 2cm, or 3cm, or combinations thereof, are placed on the proximal cylinder end to adjust length.

Once the measurement has been obtained, interrupted or running sutures can be placed for later corporotomy closure. The advantage of pre-placed sutures is the elimination of suture needles close to the area of the inflatable cylinder, diminishing the possibility of cylinder damage during corporotomy closure. Other methods of corporotomy closure include running sutures with or without a locking technique. Once the interrupted sutures are placed in the cavernostomy incision, cylinders are positioned within the dilated corpora cavernosa using the inserting tool with a distal needle to pull the cylinders into position. Once the cylinders are positioned, it is essential to visualize each one within the corpus cavernosum to ensure that no kinking is seen and that complete proximal and distal seating has taken place. The cavernostomy incision should be placed proximal enough to allow easy exit of the input tube and to minimize contact between the cylinder and the input tube. Closure of the corpus cavernosum incision is carried out with traction on the cylinder placement suture to maintain it in a flat non-kinking position and to ensure adequate seating. Following placement of the cylinder and closure of the corporotomy incision, cylinder inflation can be tested by placing fluid in each of the cylinders through the input tubes using 60ml syringes and then gently inflating the prosthesis to identify any abnormalities in position, any curvature, or any other sizing problems.

A finger is then placed in the most dependent portion of the scrotum lateral to the testicle on the right or left side. The finger is then pushed to the area of the external inguinal ring and adipose tissue in this area is dissected free using sharp and blunt dissection to expose the dartos fascia, which is thoroughly cleaned to allow pump placement. Following development of a subcutaneous pouch for the pump, the pump is positioned in the most dependent portion of the scrotum and temporarily fixed into position using a Babcock clamp. The inflatable reservoir is then placed in the previously constructed subrectus pocket and filled with an appropriate volume of normal saline or water and radiographic contrast medium. Tubing connection is carried out using quick connectors or suture tie plastic connectors. The snap-on connectors are used for the Mentor prosthesis. In a ‘re-do’ prosthesis, in which a residual tubing segment is connected to a new device piece, suture tie plastic connectors must be used. Connection is carried out by tailoring tubing to eliminate excessive length but to allow for adequate pump positioning. Rubber-shod clamps are used to compress the tubing, and the ends of the tubing, once tailored, are flushed with inflation fluid to eliminate small particles and blood clots.

After connection, the adequacy of the connection is tested. All rubber-shod clamps are removed and the device is inflated and deflated on multiple occasions to ensure adequate location, placement, and erection (Figure 45.4).

Following testing, thorough irrigation with antibiotic solution is carried out, and the rectus fascia is closed with interrupted sutures. The wound is then closed in the standard fashion with two layers of subcutaneous tissue and a subcuticular skin suture. A dry sterile dressing is applied, a Foley catheter is placed if necessary, and an ice pack is applied. Suction drains may be used at the surgeon’s discretion.

Postoperatively, patients are instructed to maintain their penis in an upward position for 4–6 weeks. Tight underwear and athletic supports are not used, in an effort to maintain the pump in its most dependent position.

**Penoscrotal approach**

Two- and three-piece inflatable penile prostheses can be implanted by a transverse or vertical penile scrotal incision (Figure 45.6). This approach has distinct advantages in obese patients and is widely used for routine penile prosthesis implantation. An incision is begun in the upper portion of the scrotum following placement of a Foley catheter. The Lone Star (Lone Star Instrument Company, Houston, TX, USA) retractor facilitates exposure with this incision. Once the skin incision has been carried out, the dissection is continued lateral to the corpus spongiosum and urethra to expose the corpora cavernosa. Incision and closure of the corpora cavernosa are similar to those described previously for the infrapubic incision. Pump placement is likewise in the most dependent portion of the scrotum just above the dartos fascia, with position maintained using a Babcock clamp. The dissection for reservoir placement, however, can be carried out with a second separate infrapubic incision but is more commonly performed through the penoscrotal incision. The scrotal skin incision is retracted to the area of the external inguinal ring, and dissection is carried out medial to the spermatic cord. The transversalis fascia is identified and punctured sharply using index finger or a Kelly clamp placed against the pubic
tubercle. Dissection is carried out using a blunt dissection. Dilatation is carried out with the index finger after incision of the transversalis fascia and with gentle blunt dissection using a large Kelly clamp. The reservoir balloon is then positioned over the index finger and placed in the perivesical space. Inflation of the reservoir is carried out with care that no back-pressure of fluid is observed. If refilling of the syringe occurs, the reservoir should be removed and further reservoir pocket dissection must be carried out. Once the reservoir is placed and inflated, and the tubing connected as previously described, the device is tested in inflation and deflation (Figure 45.7). Scrotal closure is carried out with a subcuticular suture in the standard fashion.

**Anesthesia**

The choice of anesthesia for penile prosthesis implantation varies with surgeon and patient preference. Although the majority of penile prostheses are placed with general, spinal, or epidural anesthesia, some implanting surgeons have had success with local anesthesia.\(^{34,35}\) Candidates for local anesthesia must be carefully selected, as corporal dilatation, even after infusion of local anesthetic agents, may be somewhat uncomfortable. The author prefers general and regional anesthesia, since patients are less likely to move during surgery and describe the implantation procedure as more satisfactory in post-operative interviews.

**Peri-operative care**

Peri-operative antibiotic treatment is critical in reducing the incidence of peri-operative infection and prosthetic removal. An initial peri-operative dosage of an agent effective against the most common infectious pathogens should be administered 1–2 hours prior to surgery and continued for 48 hours postoperatively.\(^{36,37}\) An aminoglycoside with a first-generation cephalosporin, a cephalosporin alone, vancomycin, or a fluoroquinolone are appropriate choices for prophylaxis of the most common infections from *Staphylococcus epidermidis*.\(^{36,38}\) Patients are discharged with 7 days of continued antibiotic therapy. The penile prosthesis remains deflated for 4 weeks while healing occurs. Prior to activation, the patient is advised to retract the pump into his scrotum on a daily basis. Tight underwear and athletic supports are avoided to maintain pump position. A return office visit for activation of the device is carried out once discomfort has resolved. Patients are advised to inflate and deflate the device on a daily basis to allow tissue expansion around the prosthesis. Most patients can then begin use of their device immediately. Satisfaction has been show to increase over 6–12 months. Patients should be encouraged to continue device cycling on a regular basis during the first year.\(^{30}\)

**Post-operative complications**

The most worrisome postoperative complication is infection. Fortunately, this complication occurs in fewer than 5% of all patients. Peri-operative prosthetic infections can, however, occur at any time in the postoperative period in patients with

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**Figure 45.6** Penoscrotal incision with a Scott retractor for penile prosthesis insertion.

**Figure 45.7** (a) A surgeon inflating an AMS inflatable penile prosthesis placed through an infrapubic approach. (b) Prosthesis deflation.
penile or other prosthetic devices. Patients continue to be at risk for hematogenously seeded infections from gastrointestinal, dental, or urological manipulations as well as from remote infections. Patients must be counseled to request antibiotic cover if remote infections occur.49 Most infections of prostheses are caused by Gram-positive organisms such as Staphylococcus epidermidis, but Gram-negative organisms such as Escherichia coli and Pseudomonas spp. are also common culprits.36,38 Severe gangrenous infections with a combination of Gram-negative and anaerobic organisms have also been identified and frequently result in significant disability and tissue loss.10–42

Patients at increased risk for peri-operative infections include those with diabetes, patients undergoing penile straightening procedures or circumcision with prosthetic implantation, patients with urinary tract bacterial colonization, and immunocompromised patients such as post-transplant patients and patients undergoing prosthesis revision or replacement.38,43 Although these patients are at increased risk, the risk of infection continues to be less than 5% and is less than 1% in studies of newer antibiotic-coated implants.44 Spinal cord injury patients have also been reported to have an especially increased risk of infections, with rates as high as 15% being reported.45 Because of a decrease in sensation, an increased risk of extrusion of semi-rigid prostheses has been reported in this group of patients. Diabetic patients with poor glycemic control may be evaluated with glycosylated hemoglobin studies to enhance diabetic control prior to prosthesis implantation and, perhaps, to decrease the possibility of infection.46 The results of these studies themselves, however, do not predict higher infection risk in diabetic patients.

Penile prosthesis infections can be divided into clinically apparent and sub-clinical penile prosthesis infections. Clinically apparent penile prostheses can be diagnosed from symptoms such as new onset of penile pain, erythema and induration overlying a prosthesis part, fever, drainage, and ultimately device extrusion. While most of these infections occur in the early peri-operative period, late device infections have been documented.59 Most infections within the first 24 months' follow-up, however, are probably infections caused by bacterial colonization at the time of surgery, with symptoms and signs beginning later. These infections are most often associated with Staphylococcus epidermidis on culture. Bacteria can, however, be cultured from asymptomatic penile prostheses and artificial urinary sphincters without evidence of infection. Licht et al. report low colony counts of Staphylococcus epidermidis from as many as 40% of uninfected penile prostheses and 36% of artificial urinary sphincters cultured at the time of revision for mechanical malfunction.47 Of these low colony count colonizations, fewer than 10% – all with high colony counts – eventually went on to penile prosthesis infection.

Sub-clinical prosthetic infections occur more frequently. These infections, which most often manifest themselves by chronic prosthesis-associated pain, are difficult to diagnose and even more challenging to treat. Device pain or migration strongly suggests that sub-clinical infection is present, requiring antibiotic therapy and frequently prosthesis removal and replacement. Parsons et al. have documented pain resolution by prosthesis removal with antibiotic irrigation and substitution of a new prosthetic device in a group of patients with prolonged isolated pain.48 They have been 90% successful in treating these prostheses with an exchange protocol including systemic antibiotics for 24–48 hours using vancomycin to target Staphylococcus epidermidis. The suspected infected prosthesis is then removed and a combination of vancomycin and protamine used for antibiotic irrigation prior to implantation of a new prosthesis. Patients are maintained on vancomycin and parenteral antibiotics for 1 week. These authors also recommend an initial trial of oral antibiotic therapy using long-term antibiotics. Following initiation of antibiotics, pain suppression should suggest continuing antibiotics for 10–12 weeks. If pain fails to resolve or rapidly returns after antibiotics, however, surgical intervention is appropriate. Parsons et al. recommend ciprofloxacin 500mg twice daily for 10–12 weeks, a regimen with an approximately 60% success rate.49 Cephalosporins are also useful with cephalaxin or cefadroxil 500mg four times daily for 10–12 weeks, with success rates of 25–30%. The findings of Licht et al. make it unlikely that intraoperative Gram staining in suspected penile prosthesis infection will be accurate.47

If a grossly infected penile prosthesis is encountered, surgical intervention along with antibiotics is of critical importance. Salvage surgery or prosthesis removal with subsequent re-implantation are current alternatives for surgical intervention. In patients with prosthesis infections that do not include significant necrosis, diabetics with significant purulence, rapidly developing infections or significant cylinder erosion, salvage procedures can be successfully performed.

It is important to choose patients carefully and to carry out rigorous surgical technique. Initially, peri-operative antibiotics are administered and all portions of the penile prosthesis as well as any additional foreign bodies are removed and wound cultures are obtained. Irrigation is then carried out in all areas where the penile prosthesis resided. This is best performed using a red rubber catheter to direct irrigation fluid into all pockets in a stepwise fashion. Mulcahy et al. recommend a sequence of irrigating solutions including kanamycin 80mg/l and bacitracin 1g/l in normal saline followed by half-strength hydrogen peroxide, half-strength providone–iodine solution, 5 liters of pressurized normal saline containing vancomycin 1g and gentamicin 80mg, half-strength providone–iodine, half-strength hydrogen peroxide, and finally another kanamycin–bacitracin solution.49 Following irrigation, gloves, instruments and drapes are changed and a new sterile prosthesis is inserted. Patients are treated peri-operatively with antibiotics, including ciprofloxacin 500mg twice daily for 4 weeks. Antibiotics can be modified on the basis of culture and sensitivity results. Brant et al. report successful salvage in 10 of 11 patients (91%) with a 21.3 month mean follow-up. Nine of 12 patients’ principal pathogen was Staphylococcus epidermidis.50 Because of the high rate of bacterial colonization of revision implants, Henry et al. have shown that modified salvage procedures with antibiotic-coated implants can dramatically lower infection risk to levels of original implants.38 They showed a colonization risk as high as 70% in replacement for mechanical problems.

The most common complication of penile prosthesis function is mechanical malfunction.11,28,51 Mechanical malfunction has declined from rates as high as 61% to levels below 5% since the 1970s (Figure 45.8). Aneurysmal dilatation of inflatable cylinders, both American Medical Systems and Mentor,
tube kinking, reservoir leakage, and pump malfunction have been limited by device modifications. Fluid leak, however, continues to be a problem for many inflatable penile prostheses. These mechanical malfunctions require replacement of the leaking portion of the inflatable portion of the prosthesis. If a non-functioning prosthesis has been in place more than 4 years, however, the author usually replaces the entire device in order to reduce further mechanical malfunction.

Semi-rigid rod penile prostheses are associated with few mechanical problems, and the most common complication associated with these prostheses is cylinder erosion through skin or urethra. Prosthesis fracture or breakage has been reported, and patients may return, 6–8 years after implantation, with complaints of decreased rigidity of their semi-rigid rod, indicating fracture of central prosthetic cylinder wires. These wire fractures cannot usually be appreciated radiographically unless the prosthesis is put on stretch once it has been explanted. Replacement of these devices is indicated when patients note decreased rigidity. Prosthesis extrusion or erosion is most common in patients with diabetes and spinal cord injury, especially those requiring catheter placement or condom collection.

Post-implantation, use of periurethral alprostadil or phosphodiesterase type 5 inhibitors has been shown to enhance the results for some patients. Alprostadil may be helpful with intromission and ultimate prosthetic function in patients with poor glans engorgement.

Conclusion

The implantation of inflatable penile prostheses is commonly performed throughout the world. This successful procedure restores erectile function in most men in whom implantation is carried out. The knowledge of the types of prostheses available, together with their advantages, disadvantages, and implantation techniques, is necessary for the skilled prosthetic management of ED. Careful discussion of these factors and the potential risks optimizes patient satisfaction. Patients should be allowed to choose prostheses from each of the classifications of prostheses available. With careful patient selection, prosthetic choice, and with currently available reliable prosthetic devices, the urologist can expect excellent patient and partner satisfaction with low morbidity.

REFERENCES

Design, development, and use of questionnaires and surveys in the evaluation and management of sexual dysfunction: erectile dysfunction

Glen W Barrisford and Michael P O’Leary

Introduction

As of 1995 approximately 152 million men worldwide were estimated to have been afflicted with some degree of male sexual dysfunction. By the year 2025, that number is expected to climb to over 322 million men. Sexual dysfunction is known to have an impact on men of all ages and freely crosses all cultural and national boundaries. Given the vast global impact of the problem, a large-scale period of intense clinical investigation has been under way since the late 1970s. Presently, we are reaping the benefits of this work by way of an improved understanding of the normal and abnormal physiology of male sexual function.

Prior to the interest established by urologists, sexual dysfunction had been a discipline that had largely fallen within the practice of psychiatric professionals. A large portion of the historic sexual dysfunction literature can be found in psychiatric publications. As one might expect, early work attributed psychogenic etiologies to many sexual disorders. Means to assess level of dysfunction were developed by the creation of comprehensive questionnaires. These surveys were aimed at evaluating the scope of the problem within the framework of established psychiatric disease. The detailed nature of these questionnaires proved to be too cumbersome for the efficient evaluation of patients in the urologic clinic. Focused but comprehensive surveys were needed by urologists. Previously established work was built upon in an effort to create more appropriate questionnaires. Three basic principles were incorporated from the psychiatric literature and were used as the foundation for contemporary urologic sexual dysfunction surveys:

1. Sexual dysfunction and satisfaction are effectively measured by patient and partner ‘self-reporting’.
2. Sexual dysfunction can be subdivided into a number of subsets or ‘domains’.
3. The ‘existence of dysfunction’ had been assumed by most surveys – the idea of creating surveys without assumptions built in was established.

The most important lesson learned from the psychiatric sexual dysfunction experience was that performance and satisfaction were determined to be best measured and evaluated by patient and partner ‘self reporting’. The questionnaires in this discussion will all have the option of being self-administered (patient–partner reporting). Second, sexual dysfunction was subdivided into a number of ‘domains’. Each of these domains is a specific component of sexual dysfunction and is evaluated by a subgroup of questions within a given survey. For example, a survey with 20 questions may allocate five questions to each of the following domains: erectile function, ejaculatory function, sexual interest, and satisfaction. The domain-specific approach allows the clinician to hone in more specifically on the problem. Lastly, it was assumed that all patients who would be completing questionnaires would have sexual dysfunction. An assumption or expectation of dysfunction universally existed. Therefore, the questions and surveys were designed with this assumption in mind. It was O’Leary who suggested that a questionnaire be designed in a ‘non-evaluative’ way so that the function and the impact of that function could be measured autonomously. This was a major advance in the evolution of male sexual function surveys. By using these building blocks, concise surveys were designed with the intention of obtaining maximum information with minimal expenditure of office and staff time.

The remainder of the discussion here addresses the specific tools available to the urologist to evaluate male patients with concerns regarding sexual dysfunction.

Addressing dysfunction

Sexual dysfunction can often be an exasperating problem for patients and partners. Anxiety and embarrassment can hamper the discussion between patient and clinician. As a consequence, male sexual dysfunction is a problem that has largely gone under-diagnosed and frequently goes untreated. The clinician should aim to initiate this discussion and offer the patient an opportunity to address any concerns. One way to ease into this discussion is to present the patient with a questionnaire to review and complete prior to meeting with the clinician. This allows the patient to consider concerns that might otherwise go unaddressed once face-to-face with the
Defining male sexual dysfunction

Male sexual dysfunction can be categorized into a number of domains. The most classically recognized domains are: desire, erectile and ejaculatory function, orgasmic function, satisfaction, and bother. Surveys are generally designed to address each of these entities as a separate component. However, many of these domains overlap and are interdependent. For example a person with erectile difficulty may require intense stimulation to achieve and maintain an erection. The intense stimulation may secondarily result in premature ejaculation. The erectile and ejaculatory function may subsequently affect desire, patient–partner satisfaction, and bother.

Initial evaluation

The initial evaluation of a patient presenting with sexual dysfunction includes a complete medical, sexual, and psychosocial history and a complete physical examination. Upon obtaining the history, the physician should make every effort to provide a comfortable and supportive setting, the assurance of confidentiality, and the avoidance of judgementalism. The patient should be allowed to feel in control of the discussion. Under these circumstances patients will tend to provide more complete explanations and allow the introduction of sensitive topics into the discussion. Additional diagnostic and laboratory evaluation will be directed by the findings of the history and physical examination.

Development of surveys

In an effort to create questionnaires with statistical value, efforts have been made to develop ‘validated’ surveys. The term ‘validated’ was originally used in the discipline of psychometrics. Psychometrics is a branch of psychology that deals with the design, administration, and interpretation of quantitative tests for the measurement of psychological variables such as intelligence, aptitude, and personality traits.

When creating a survey, a condition of interest is selected. Subsequently, a complete battery of items is developed to describe all aspects of the chosen condition. At this point a formal statistical process is used to narrow the survey into a workable questionnaire. Once this is completed the questionnaire is tested in populations with the condition of interest in an effort to validate the survey. To be validated means that the questionnaire accurately measures what it intends to measure. Responses on individual questions may be scaled independently (from 0 to 5). This is known as a Likert scale. Alternatively, a visual analog scale can be used by having the patient mark on a line between 0 and 10. This method is similar to that used for the assessment of pain levels in post-operative patients.

Heiman and Quirk et al. have defined essential criteria for validated instruments:

- reliability;
- test–retest reliability;
- internal consistency;
- test validity;
- concurrent validity;
- divergent validity;
- sensitivity;
- specificity;
- capacity; and
- receiver operating characteristics (ROC).

Reliability is often referred to as an ‘inverse measurement of error’. To be reliable implies that a survey yields the same or comparable results in different clinical experiments or statistical trials. Therefore, a survey with high reliability is considered to provide consistent information.

The test–retest reliability applies when a given survey is repeatedly applied to the same population over a period of several weeks. Thus, the test–retest reliability is a measurement of the stability of the factors over time. Similarly, the internal consistency refers to the uniformity of an item within a domain.

Test validity, concurrent validity, and divergent validity are values that measure the degree to which a test will actually measure what it is intended to measure. Sensitivity is the ability of a given test to differentiate between people with and without dysfunction. Specificity is a measure of discriminating between people that are not affected by the disease or condition. Capacity refers to the ability of a given instrument to detect changes in the conditions measured with the advent of treatment.

Receiver operating characteristics curves (ROC curves) have been used in the analysis of a given instrument to assess the ability to correctly classify a patient’s status based upon a score in a given domain. Alternatively stated, the ‘area under the curve’ (AUC) is an appraisal of the discriminant ability of a given questionnaire.

Various additional statistical measurements have been applied to validated questionnaires. However, the preceding represents the nucleus of essential items applied to most surveys in use.

Validated surveys

A number of surveys have been developed and validated secondary to the increased interest in the field of male sexual dysfunction. In an effort designed to review and examine rigorously the available surveys, the Second International Consultation on Sexual Dysfunction (Paris) prepared specific guidelines with respect to the use of a select group of validated instruments. The scope of the recommendations included surveys used to evaluate both sexes. This discussion considers only those relevant to the evaluation of male sexual dysfunction.
Among validated surveys, a two-tiered system was developed. Those in the top echelon consisted of 'highly recommended' surveys, and those in the second tier were considered 'additional recommended' surveys. The stratification was based upon reliability; internal consistency; number of domains evaluated; ease; duration, and mode of transmission; discriminative validity; sensitivity; and specificity. All of the questionnaires recommended were self-administered. However, a number of the surveys could be administered during a clinical interview (CI) as well. A detailed review of this two-tiered system follows here. In addition, a discussion of 'additional valuable' instruments is included. This consists of a number of surveys that have been deemed to be highly useful for clinicians based upon the authors’ own rigorous review of the remaining sexual dysfunction surveys.17

Highly recommended surveys

Change in Sexual Function Questionnaire

The Change in Sexual Function Questionnaire (CSFQ) is a survey that can be administered in CI or self-report (SR) formats. The CI version contains 36 items while the SR version contains 14 items. They can be completed in 20 and 5 minutes, respectively. Versions have been created for use with men or women. This particular questionnaire is tailored to address five domains of dysfunction: sexual desire and interest, sexual desire and frequency, sexual pleasure, sexual arousal and excitement, and orgasm completion. In its original form this survey was designed to detect alterations in sexual function secondary to the administration of medication or changes related to illness. The CSFQ is appropriate for both heterosexual and homosexual men. This survey carries a satisfactory reliability (0.64–0.80), and values that have been considered ‘acceptable’ for the concurrent and discriminative validity.18,19 This survey was noted to be particularly useful in demonstrating changes in sexual function secondary to antidepressant medications.20 Normal values have been established and can be used for comparison. Validated versions exist in English and Spanish, but translated versions have been established with linguistic validation in French, German, Dutch, Italian, Swedish, Finnish, and French Canadian.18

Derogatis Interview for Sexual Functioning

The Derogatis Interview for Sexual Functioning (DISF) can be administered in a CI version or a SR (DISF-SR) version and is applicable for both men and women. The main objective of this survey is to evaluate the current sexual function of the patient. Twenty-five items address five domains of interest: sexual cognition and fantasy, sexual arousal, sexual behavior and experiences, orgasmic function, and sexual desire/relationship. This test is designed to be interpreted at three tiers: individual items, individual domains, and the summary (total score). This survey can be completed in approximately 15 minutes. The DISF-SR carries a test–retest reliability of 0.8–0.9, and an internal consistency of 0.74–0.8. This survey has been validated and is available in 10 languages.

Golombok–Rust Inventory of Sexual Satisfaction

The Golombok–Rust Inventory of Sexual Satisfaction (GRISS) is a 28-item survey that is designed to evaluate the existence and severity of sexual problems among individuals or couples. When given as a combined survey for couples it consists of 56 items. In the combined survey 12 domains are evaluated, with two being common to both sexes while the other 10 consist of five that are specific to each sex. The 28-item male version evaluates the five domains of premature ejaculation, erectile dysfunction, avoidance, non-sensuality, and dissatisfaction. The two additional common domains are frequency of sexual contact and non-communication. The survey is reported with an aggregate score that summarizes the sexual function and relationship quality. This survey can be administered in 15 minutes. The range of internal consistency is 0.61–0.83, while the test–retest reliability ranges from 0.47 to 0.82. Normal values have been established, and versions are available in English and Dutch.

International Index of Erectile Function

The International Index of Erectile Function (IIEF) was primarily designed to evaluate erectile function and quality. It is a 15-item survey that can be completed in approximately 15 minutes. The origin of this survey lies within the initial clinical trials of sildenafil.24,25 However, those trials offered wide exposure and use, leading to the current popularity of the IIEF so that it is now one of the most common surveys used in clinical practice. Five domains are evaluated: erectile function, orgasmic function, sexual desire, sexual satisfaction, and overall satisfaction. The internal consistency ranges from 0.73 to 0.95 and the test–retest reliability from 0.64 to 0.84. Standardized cut-off values are available for comparison. Severe erectile dysfunction (ED) is noted at scores 6–10, moderate ED at scores 11–16, mild-to-moderate ED at scores 17–21, and mild ED at scores 22–25.28 Scores in the range of 26–30 represent normal sexual function. This survey has been validated and is available in 32 languages.

The erectile function of the IIEF is referred to as the IIEF-6. This six-item mini-survey can be completed in less than 10 minutes. It carries an internal consistency of 0.92–0.99 and a test–retest reliability of 0.64. This survey has most often been used in clinical trials. A score of 25 or greater represents normal erectile function. The sensitivity and specificity are 89% and 93%, respectively.

Recommended surveys

Arizona Sexual Experience Scale

The Arizona Sexual Experience Scale (ASEX) is another SR survey that can be administered to men and women. This five-item questionnaire addresses five domains of male sexual function: sexual drive, sexual arousal, erectile function, orgasmic function, and sexual satisfaction. The ASEX is scored from 5 to 30 and can be completed in 5–10 minutes. A higher score indicates a greater degree of sexual dysfunction. The internal consistency is 0.81 and the test–retest reliability is 0.69–0.84. A score of 11 or less indicates the absence of sexual
dysfunction. Sensitivity and specificity are 100% and 52%, respectively. A number of clinical trials have incorporated this survey as a primary tool.

**Brief Male Sexual Function Inventory**

The Brief Male Sexual Function Inventory (BSFI)

The Brief Male Sexual Function Inventory (BSFI)\(^*\) is another SR survey that was initially designed to evaluate male sexual dysfunction. It was modeled after the American Urological Association (AUA) Symptom Index for benign prostatic hyperplasia. It was validated in a similar fashion.\(^{31,28}\) The AUA symptom index is familiar to most urologists and served as an excellent model upon which to design a sexual dysfunction survey. The BSFI is an 11-item questionnaire that evaluates five domains and takes approximately 10 minutes to complete. The domains are sexual drive (two items), erectile function (three items), ejaculation (two items), perception of a problem (three items), and overall satisfaction (one item). The internal consistency is 0.62–0.95 and the test–retest reliability varies from 0.79 to 0.89. Although no cut-off points have been developed at this time, it has been widely used in clinical trials.

**Derogatis Sexual Functioning Inventory**

The Derogatis Sexual Functioning Inventory (DSFI)\(^*\) is a 245-item survey that requires approximately 90–120 minutes to complete and address 10 domains of function. Although this survey is an extensive, complete survey it is not practical for the outpatient setting given the time required to complete the survey. It is most often used in the evaluation of couples and does not possess normal values or cut-off points.

**Additional valuable surveys**

**Self-Esteem and Relationship Questionnaire**

The Self-Esteem and Relationship Questionnaire (SEAR)\(^{39}\) is a 14-item survey that addresses the three domains of sexual relationship, self-esteem, and overall relationship. It was originally developed with the objective of measuring confidence, self-esteem, and the quality of sexual relationships in men with ED.\(^{29,30}\) This survey can be completed in approximately 15 minutes and is often utilized in clinical trials.\(^{31–34}\) The internal consistency is 0.76–0.93 and the test–retest reliability is 0.57–0.79. Presently no norms or cut-offs have been established for comparison.

**The Sexual Health Inventory for Men**

The Sexual Health Inventory for Men (SHIM)\(^{35}\) is another brief survey that is often used in clinical trials but also has found a place in the urologic clinic. In our practice at the National Naval Medical Center, patients complete both the SHIM and AUA symptom score while waiting to see the urologist. This is a five-item survey that is essentially a shortened version of the IIEF,\(^{21}\) which addresses the domains of erectile function and intercourse satisfaction. This survey can be easily completed in less than 10 minutes and serves as an excellent screening tool to identify men who may warrant further discussion on the topic of sexual dysfunction. The sensitivity and specificity are 96% and 88%, respectively. Although this survey has no established consistency or reliability, the survey has an established cut-off point. Men who score less than 21 are considered to have ED, and the degree of ED is measured along a spectrum using the total score: 1–7 suggests severe ED, 8–11 moderate ED, 12–16 mild-to-moderate ED, and 17–21 mild ED.

**The Male Sexual Health Questionnaire**

The Male Sexual Health Questionnaire (MSHQ)\(^{36}\) is a 25-item survey that addresses the three domains of erectile function, ejaculation, and sexual satisfaction. This survey can be completed in approximately 20 minutes and has been used in the clinical setting to evaluate male sexual dysfunction. The internal consistency ranges from 0.84 to 0.93 and the test–retest reliability from 0.85 to 0.94. Neither cut-off points nor normal values have been established for the MSHQ.

**The Sexual Encounter Profile**

The Sexual Encounter Profile\(^{37–39}\) has gained widespread popularity as a measure in clinical trials used to assess the effectiveness of erectogenic medications, most notably tadalafil. This survey consists of five items and can be completed in less than 5 minutes. This survey appears commonly in pharmaceutical company literature to support product efficacy. However, to the best of our knowledge this survey has not been validated. The two most commonly studied questions include SEP question 2: ‘Were you able to insert your penis into your partner’s vagina?’ and SEP question 3: ‘Did your erection last long enough for you to have successful intercourse?’ Although the statistical significance of this survey has not been clearly demonstrated, it warrants mention here given the likelihood that the urologist will encounter it in pharmaceutical literature.

**Conclusion**

At one time sexual dysfunction was largely considered a disease of psychogenic origin. As a consequence it became a clinical interest among the psychiatric profession. However, the past 30 years of research has spawned a large interest in understanding the organic etiology of sexual dysfunction. As a result, we now have a greater understanding of the anatomy and physiology of male sexual function. This body of knowledge, coupled with pharmacological innovation and the development of validated questionnaires, has exponentially increased the interest in male sexual dysfunction in the urologic community. These developments have allowed the identification of patients with organic sexual dysfunction, and have simultaneously provided a means to measure the response to therapy. The vast number of surveys available is a clear demonstration of the rising clinical and research interest. Although only a small number of surveys have been discussed in this chapter, it is our goal to expose the reader to a useful cross-section of instruments. This exposure will allow the
clinician or researcher to select a tool most useful for their specific needs.

Validated surveys have sustained rigorous statistical review with respect to the most common measures. Although many surveys do not possess established cut-off points or normal values, the many measures of each survey can be used for comparison. For example, a survey with an internal consistency of 10% can not possess the same statistical strength as one with 90%. Conversely, it is important to understand that surveys are imperfect tools with strengths and weaknesses in different areas. Selection of a survey must begin with the question of the purpose. If one is seeking a screening tool to be used in the outpatient clinic to assess for the presence of male sexual dysfunction, the BSFI might be a better choice than the IIEF. However, if a patient presents with a complaint of ED, the IIEF-6 would be preferred. Familiarity with an array of validated surveys is useful because no single instrument is universally applicable.

Validated surveys have strived to be brief and self-reported while addressing the main domains of male sexual dysfunction. However, they are not intended to replace a complete history and physical examination, appropriate laboratory evaluations, or physician judgement and experience. Although these surveys can help to identify dysfunction they fail to offer etiologic origin. Validated surveys carry many imperfections, which prevents them from providing the ultimate solution to male sexual dysfunction. However, their appropriate development and use provides another tool for the clinician to guide the evaluation and management of men with sexual dysfunction.

REFERENCES


33. Cappelleri JC, Bell SS, Althof SE, et al. Comparison between sildenafil-treated subjects with erectile dysfunction and control


Assessment of male ejaculatory disorders

Raymond C Rosen, Stanley E Althof, and Tara Symonds

Introduction

Prevalence and impact of ejaculatory disorders
Orgasmic and ejaculatory disorders in men are highly prevalent, although less well understood or recognized than erectile dysfunction (ED). Epidemiological studies have shown that both premature ejaculation (PE) and ejaculatory dysfunction (EjD) are common in men. Recent studies have shown that about 30% of men in each age category have premature ejaculation, whereas the prevalence of EjD increases to more than 50% in the 70 and over age group. Studies have shown that at least half of men over age 60 with benign prostatic hyperplasia (BPH) and lower urinary tract symptoms have decreased or absent ejaculation. Additionally, EjD is commonly seen after pelvic or prostate surgery, and is a reported side-effect of various medicines (e.g. alpha-blockers, such as tamsulosin, and selective serotonin reuptake inhibitors). One recent study showed a significant degree of bother or psychological distress associated with delayed or absent orgasm or ejaculation in men, as has also been demonstrated with PE. Unfortunately, in contrast to PE, few treatments have been described for EjD. Clinically, the condition is largely unrecognized.

Instruments for assessing male sexual function
Patient self-assessment questionnaires are necessary and important tools in assessing sexual function in a clinical setting. Validated questionnaires, also known as patient-reported outcomes (PROs) play an integral role in the diagnosis and treatment of male sexual dysfunctions. They are used to:

- identify or diagnose men who suffer from sexual problems;
- assess the severity of the dysfunction;
- measure improvement or satisfaction with treatment;
- examine the impact of the dysfunction on the person’s quality of life (e.g. relationship satisfaction, mood, sexual confidence); and
- study the impact of the dysfunction on the partner and his or her quality of life.

The most widely used PROs in the assessment of male sexual function include:

- the International Index of Erectile Function (IIEF; 15 items; five domains of male sexual function: erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction);
- the Brief Sexual Function Inventory (11 items that focus on sexual drive, erection, ejaculation, perceptions of problems in each of these areas, and overall satisfaction); and
- the International Continence Society Sex Questionnaire (four items assessing erectile function, ejaculatory function, pain or discomfort during ejaculation, and the extent that urinary symptoms spoil the patient’s sex life).

The Danish Prostate Symptom Score Sex questionnaire has also been used to assess erection, ejaculation, pain or discomfort during ejaculation, and the bothersomeness of each of these items.

In this chapter we describe new PRO instruments that specifically focus on disorders of ejaculation, both rapid and delayed. These new instruments will undoubtedly contribute significant new information to our understanding of these disorders. We will begin by discussing PE, and recent assessment measures of that dysfunction. We then consider EjD and one new measure for assessing this disorder.

Definitions of premature ejaculation and problems with the current definitions
A universally accepted definition of PE remains to be established. To date there are at least eight definitions of PE offered by different professional organizations or researchers (Table 47.1). All but one were derived from the consensus opinion of experts, or from clinical wisdom; only that of Waldinger et al. is the by-product of scientific data collection from a large observational study from the general population. All but two definitions suffer from excessive vagueness, lack of precision and undue subjectivity on the part of the diagnostician. For example, let us examine the definition of PE from the American Psychiatric Association:

- Persistent or recurrent ejaculation with minimal sexual stimulation before, on or shortly after penetration, and before the person wishes it.
Table 47.1 Definitions of premature ejaculation

<table>
<thead>
<tr>
<th>Definition</th>
<th>Offered by</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent or recurrent ejaculation with minimal sexual stimulation, before, on or shortly after penetration and before the person wishes it. The condition must also cause marked distress or interpersonal difficulty and cannot be due exclusively to the direct effects of a substance.</td>
<td>American Psychiatric Association&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
<tr>
<td>For individuals who meet the general criteria for sexual dysfunction, the inability to control ejaculation sufficiently for both partners to enjoy sexual interaction, manifest as either the occurrence of ejaculation before or very soon after the beginning of intercourse (if a time limit is required, before or within 15 seconds) or the occurrence of ejaculation in the absence of sufficient erection to make intercourse possible. The problem is not the result of prolonged absence from sexual activity.</td>
<td>International Statistical Classification of Disease, 10th ed&lt;sup&gt;16&lt;/sup&gt;</td>
</tr>
<tr>
<td>The inability to control ejaculation for a ‘sufficient’ length of time before vaginal penetration. It does not involve any impairment of fertility, when intravaginal ejaculation occurs.</td>
<td>European Association of Urology (Guidelines on Disorders of Ejaculation)&lt;sup&gt;12&lt;/sup&gt;</td>
</tr>
<tr>
<td>Persistent or recurrent ejaculation with minimal stimulation before, on, or shortly after penetration, and before the person wishes it, over which the sufferer has little or no voluntary control, which causes the sufferer and/or his partner bother or distress.</td>
<td>International Consultation on Urological Diseases&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ejaculation that occurs sooner than desired, either before or shortly after penetration, causing distress to either one or both partners.</td>
<td>American Urological Association (Guideline on the Pharmacologic Management of Premature Ejaculation)&lt;sup&gt;15&lt;/sup&gt;</td>
</tr>
<tr>
<td>The man does not have voluntary, conscious control, or the ability to choose in most encounters when to ejaculate.</td>
<td>Metz and McCarthy&lt;sup&gt;14&lt;/sup&gt;</td>
</tr>
<tr>
<td>The Foundation considers a man a premature ejaculator if he cannot control his ejaculatory process for a sufficient length of time during intravaginal containment to satisfy his partner in at least 50 percent of their coital connections.</td>
<td>Masters and Johnson&lt;sup&gt;13&lt;/sup&gt;</td>
</tr>
<tr>
<td>Men with an IELT of less than 1 minute (belonging to the 0.5 percentile) have ‘definite’ premature ejaculation, while men with IELTs between 1 and 1.5 minutes (between 0.5 and 2.5 percentile) have ‘probable’ premature ejaculation. In addition, an additional grading of severity of premature ejaculation should be defined in terms of associated psychological problems. Thus, both definite and probable premature ejaculation need further psychological subclassification in nonsymptomatic, mild, moderate, and severe premature ejaculation.</td>
<td>Waldinger et al.&lt;sup&gt;17&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

IELT, intravaginal ejaculatory latency time

- The disturbance causes marked distress or interpersonal difficulty.
- The PE is not due exclusively to the direct effects of a substance.

How would a clinician objectively define ‘minimal sexual stimulation’ or ‘shortly after penetration’ or ‘before the person wishes’ or ‘marked distress or interpersonal difficulty’? One clinician’s interpretation of this definition is likely to differ from another clinician’s interpretation.

Despite the convincing criticisms leveled at the eight definitions of PE (excessive vagueness, imprecision, and subjectivity) there is significant overlap among them. Four common factors emerge from the proposed definitions: intravaginal ejaculatory latency time (IELT), perceived control, distress, and interpersonal difficulty (related to the ejaculatory dysfunction).

Given these common factors, the issue becomes whether a diagnosis of PE should be uni-dimensional,<sup>16-20</sup> based primarily on a defined IELT threshold, or multi-dimensional, utilizing a defined IELT threshold and the variables of perceived lack of control, poor sexual satisfaction, and distress.<sup>21,22</sup> Recent publications of observational data in men with and without PE have clarified the answer to this controversy.<sup>23-25</sup>

The data suggest that the diagnosis of PE should be multi-dimensional and include clearly defined thresholds of IELT, the man’s perceived control, sexual satisfaction, and distress. Perceived control, sexual satisfaction, and distress can be assessed via brief self-administered questionnaires with validated cut-off points. There remains some controversy as to the IELT threshold necessary to diagnose PE; further data analysis will probably resolve this debate.

Patient-reported outcomes for premature ejaculation

Table 47.2 lists the PROs available to identify or diagnose men with PE and PROs for detecting change when treating men with PE. The psychometric properties of each measure are described as well. Table 47.3 was compiled by reviewing the
### Table 47.2 Psychometric properties of measures of premature ejaculation

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Population</th>
<th>Factor analysis</th>
<th>Reliability</th>
<th>Validity</th>
<th>Responsiveness</th>
<th>MID</th>
<th>Diagnostic tests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Internal consistency</td>
<td>Test–retest</td>
<td>Convergent–divergent</td>
<td>Known groups</td>
<td></td>
</tr>
<tr>
<td>CIPE</td>
<td>n=169; Mean IELT: 1.6 (SD 1.2) minutes; 61% lifelong; 39% acquired</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>Single-Item PROs</td>
<td>Two groups: n=1587; n=166 DSM-IV clinician diagnosis; DSM-IV clinician diagnosis plus IELT 2 minutes &gt;50% intercourse episodes</td>
<td>n/a</td>
<td>n/a</td>
<td>✓</td>
<td>×</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>IPE</td>
<td>Study 1: n=147 lifelong PE; DSM-IV clinician diagnosis. IELT mean 1.92 (SD 2.98) minutes. Study 2: n=939 acquired or lifelong PE; DSM-IV clinician diagnosis, IELT mean 3.9 (SD 37.4) seconds</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>×</td>
</tr>
<tr>
<td>MSHQ-EjD</td>
<td>n=1245 US men; n=179 homosexual or bisexual men; n=6909 US men with lower urinary tract symptoms and benign prostatic hyperplasia; no details on PE status within these samples</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>×</td>
</tr>
<tr>
<td>PEDT</td>
<td>n=292; IELT 66 (SE 1.78) seconds; n=309 self-reported PE; IELT 279.4 (SE 19.22) seconds</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>×</td>
<td>×</td>
</tr>
</tbody>
</table>

MID, minimum important difference; PE, premature ejaculation; CIPE, Chinese Index of Premature Ejaculation; Single-Item patient-reported outcomes (PROs), Control, Sexual Satisfaction, personal distress and interpersonal difficulty; IPE, Index of Premature Ejaculation; MSQ, Male Sexual Quotient; MSHQ-EjD, Male Sexual Health Questionnaire-Ejaculatory Dysfunction; PEDT, Premature Ejaculation Diagnostic Tool. SE, standard error; SD, standard deviation; DSM, Diagnostic and Statistical Manual; ✓, feature demonstrated; ×, feature not demonstrated.
Table 47.3 Psychometric properties of premature ejaculation measures

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Population</th>
<th>Factor analysis</th>
<th>Reliability</th>
<th>Validity</th>
<th>Responsiveness</th>
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<tr>
<td></td>
<td></td>
<td>Internal consistency</td>
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<td>Convergent or divergent</td>
<td>Known groups</td>
</tr>
<tr>
<td>CIPE</td>
<td>n = 169; mean IELT 1.6 (SD 1.2) minutes; 61% lifelong; 39% acquired</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>✓</td>
</tr>
<tr>
<td>Single-item PROs</td>
<td>Two groups: n = 1587; n = 166 DSM-IV clinician diagnosis plus IELT, 2 minutes &gt; 50% intercourse episodes</td>
<td>n/a</td>
<td>n/a</td>
<td>✓</td>
<td>×</td>
</tr>
<tr>
<td>IPE</td>
<td>Study 1: n = 147 lifelong PE; DSM-IV clinician diagnosis. IELT mean 1.92 (SD 2.98) minutes. Study 2: n = 939 acquired or lifelong PE; DSM-IV clinician diagnosis; IELT mean 3.9 (SD = 3.74) seconds</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>MSHQ-EjD</td>
<td>n = 1245 US men; n = 179 homosexual or bisexual men; n = 6909 US men with lower urinary tract symptoms or benign prostatic hyperplasia; no details on PE status within these samples</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>PEDT</td>
<td>n = 292; IELT 66 (SE 1.78) seconds; n = 309 self-reported PE; IELT 279.4 (SE 19.22) seconds</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

PE, premature ejaculation; CIPE, Chinese Index of Premature Ejaculation; IPE, Index of Premature Ejaculation; MSHQ-EjD, Male Sexual Health Questionnaire-Ejaculatory Dysfunction; PEDT, Premature Ejaculation Diagnostic Tool. ✓, feature demonstrated; ×, feature not demonstrated

literature, and only those measures for which the reliability and validity is documented have been included.

Patient-reported outcomes to identify or diagnose premature ejaculation

There are three measures available to diagnose PE. The first, the Chinese Index of Premature Ejaculation (CIPE) has five items, which assess perceived time to ejaculation from intromission, ability to prolong intercourse time, sexual satisfaction, partner satisfaction, and anxiety or depression related to sexual activity. This measure does not appear to have had any psychometric analyses conducted before the scoring system to diagnose absence or presence of PE. Although further validation appears necessary, the CIPE may be used to identify men with PE, although it is not recommended as an outcome measure.

The Arabic Index of Premature Ejaculation (AIPE) is a seven-item self-report measure that assesses sexual desire, erectile function, ejaculation time and control, and mood. Comparing the scores of clinician-diagnosed men with and without PE, the sensitivity and specificity of the AIPE was 0.98 and 0.88, respectively. No information regarding reliability, treatment responsiveness, and meaningful differences is available. The limitations of the tool are that it is only in Arabic, it was based on a relatively small sample of subjects, and important psychometric parameters have yet to be determined.

The third PRO, the Premature Ejaculation Diagnostic Tool (PEDT) is a five-item measure that evaluates difficulty in delaying ejaculation, ejaculating before the person wishes, ejaculating with little stimulation, frustration related to ejaculating prematurely, and concerns about partner being sexually unfulfilled. The items have good reliability and validity. Additionally, the PEDT has excellent sensitivity and specificity and makes an ideal diagnostic tool.

The limitation to using questionnaires in busy clinical practices is the time required to have the patient complete the measure and the time necessary to score the PRO and make the diagnosis. However, all three measures are brief and are quickly completed and scored. They are less intrusive and burdensome than asking patients to time lovemaking, and they provide an immediate decision regarding diagnosis.
Patient-reported outcomes for determining treatment effects

There are five measures developed to assess the impact of treatment on men with PE. A summary of the development and validation of each PRO is given in Table 47.3.

The Premature Ejaculation Profile (PEP) contains four questions assessing perceived control over ejaculation, satisfaction with sexual intercourse, personal distress related to ejaculation, and interpersonal difficulty related to ejaculation. Each item has been validated and has shown robust psychometrics. An assessment of the items’ convergent and divergent validity needs to be considered, as does a criterion for showing a meaningful change such as minimum important difference (MID) or responder definition.

The advantage of the PEP is its brevity. However, this may also be a limitation since each domain (control, satisfaction, distress, and interpersonal difficulty) consists of only one question, which may have an impact on the reliability of the items and limit the sensitivity of each domain.

The Index of Premature Ejaculation with three domains covering control, sexual satisfaction, and distress, has also shown strong psychometric properties. Responsiveness has yet to be shown and a minimal important difference/responder definition needs to be defined.

There are other measures mentioned in the literature; however, validation data are very sparse or non-existent. The PEQuest was developed to investigate cognitive and partner-related factors in PE. However, apart from information about how it was developed, there is limited information given as to its validation. The Yonsei-Sexual Function Inventory-II was similarly developed to assess various factors related to PE (performance anxiety, patient and partner satisfaction, sexual desire, and overall sexual function) but, again, there is no validation information in the literature to defend the measures used to assess outcome in PE clinical trials.

Ejaculatory dysfunction

A less widely understood or recognized problem in men is EjD. This refers to the loss of force or volume or to delay or complete absence of ejaculation. This problem is highly age-related, like ED, and is commonly reported in older men or men who have benign or malignant prostate disease. The emission and ejaculation of semen can take place with or without the subjective experience of orgasm.

The physiologic and pathophysiologic mechanisms of ejaculatory function are not well understood, although current studies of neurophysiological measures are under way. Emission (i.e., deposition of seminal fluid and sperm from the distal epididymis, vas deferens, seminal vesicles, and prostate gland into the posterior urethra) and ejaculation (i.e., expulsion of seminal contents through the urethral meatus) are controlled by the sympathetic and somatic nervous systems. Both emission and ejaculation involve contractile processes. Central serotonergic neurotransmission may also play a role in ejaculation. Interestingly, the stimulation of different serotonin (5-hydroxytryptamine, 5-HT) receptor subtypes can result in an increase or decrease in the ejaculatory latency time. In the rat, postsynaptic 5-HT-1A and 5-HT-2C receptors appear to play a role in ejaculatory behavior. Based on the results of animal studies, Waldinger suggested that hypoactivity of 5-HT-2C receptors or hypersensitivity of 5-HT-1A receptors (or both) may be responsible for premature ejaculation in humans.

Male Sexual Health Questionnaire

To address the need for an instrument to assess specific aspects of ejaculation in older men, a new self-administered questionnaire, the 25-item Male Sexual Health Questionnaire (MSHQ), was recently developed and validated. The MSHQ, which has domains for erection (three items), ejaculation (seven items), and sexual satisfaction (six items), provides a more in-depth assessment of ejaculatory function and sexual satisfaction than the IIEF and other instruments. The ejaculation domain of the MSHQ assesses loss of ejaculation, delayed ejaculation, the force of the ejaculation, the amount of semen ejaculated, pleasure associated with ejaculation, and pain or discomfort during ejaculation. In validation studies, the three domains of the MSHQ demonstrate a high degree of internal consistency, test–retest reliability, and construct validity as well as the ability to differentiate between men with lower urinary tract symptoms and sexual dysfunction and healthy men.

Of the three domains of the MSHQ, the ejaculation domain has the most significant correlation with severity of lower urinary tract symptoms. Linguistic validation studies of the MSHQ have been completed. The MSHQ is also being used to assess sexual function in a national survey of US men. A US observational BPH Registry is collecting data on patient outcomes and the relationship of lower urinary tract symptoms and BPH with sexual dysfunction and data from placebo-controlled clinical trials of the effects of treatment with alfuzosin 10mg (on demand) on sexual function in men with lower urinary tract symptoms and BPH. The results of these studies will provide valuable new information on EjD in the general population of men and specifically in those men with BPH and lower urinary tract symptoms.

Male Sexual Health Questionnaire – Short Form

An abridged four-item MSHQ for assessing EjD – MSHQ-EjD Short Form – with three ejaculatory function items and one ejaculation bother item has recently been developed. This new screening measure demonstrates a high degree of internal consistency, reliability, and construct validity, together with an ability to discriminate between men with no lower urinary tract symptoms or mild symptoms and those with moderate-to-severe symptoms. This four-item questionnaire adheres to the measurement properties for patient-administered outcome instruments as described in draft guidance issued in 2006 by the US Food and Drug Administration, and it should provide healthcare professionals with an easy-to-use instrument for assessing EjD in everyday clinical practice.
Overall, the topic of ejaculatory dysfunction (EjD) has been neglected in comparison with other common male disorders, notably ED and PE. In part, this may be due to the lack of available treatments for EjD. However, the recent availability of a validated questionnaire measure (MSHQ) for assessing components of EjD, and the recent publication of a brief, screening tool (MSHQ-Short Form) could raise awareness and stimulate research or practice in this area. Based on the results of the Multinational Survey of The Aging Male (MSAM-7), men with problems of ejaculatory dysfunction were almost as bothered as men with ED by the presence of this problem. Specifically, more than half the men in that study with EjD reported being bothered by the problem. Since loss of ejaculatory function is a common result following prostatectomy surgery, the scale may have particular benefit in assessing EjD prior to or following prostatectomy surgery. Additionally, the scale may be of value in assessing the response to treatment in sexually active men being treated with alpha-blockers or 5-alpha-reductase inhibitors.

Future directions

Ejaculatory disorders (PE, EjD) have received less attention than ED in both the clinical and research literature in recent years. As a result, measurement approaches are less developed, and adequate PROs for PE and EjD have only recently become available. The availability of these new measures, it is anticipated, will contribute substantially to the development of new management approaches in the coming years. We anticipate that these new PRO scales will be used increasingly in preference to stop-watch or other objective measures, since they more accurately reflect the patient’s and partner’s views of the sexual problem and area of greatest distress. In the PE literature, this has been shown to be the domain of ejaculation control. For EjD, it is the loss of force and volume of ejaculation that causes maximum distress for patients. Sensitive and reliable PRO scales such as those described in this chapter are the optimal means for assessing these effects.

Further studies are needed to characterize fully the psychometric properties of the scales described in this chapter. Cross-cultural studies are urgently needed, and further studies of treatment sensitivity would enhance our understanding of each of these measures. The clinical utility of these measures also needs to be further addressed, in addition to the profile of responses in patients with chronic medical or psychiatric conditions. Medication effects also need to be more fully investigated.

In summary, ejaculatory problems (PE, EjD) are highly prevalent and potentially bothersome sexual problems in men. Greater attention has been given to erection problems in recent years, although studies have indicated that ejaculatory problems may be almost as common and a potential source of distress for many men and their partners. New questionnaires and validated assessment tools have been developed, and these are recommended for clinical and research purposes.

REFERENCES

Clinical trial design for erectile dysfunction

Introduction

It is estimated, from 2001–2002 data, that erectile dysfunction (ED) was self-reported by one in five men in the USA. However, the prevalence may be higher, since the rate of ED identified by the International Index of Erectile Dysfunction five-item index (IIEF-5) has been shown to be nearly twice that of self-reported ED. During the past 20 years there has been fundamental change in the way in which ED is treated and also the attitudes of both the medical profession and the general population to this condition. Prior to 1995, when the first treatment for ED (intracavernosal alprostadil) was approved in the USA by the Food and Drug Administration, treatment of ED had been limited to psychotherapy and vacuum tumescence devices, and many considered the condition to be an inevitable consequence of the aging process. However, further understanding of the physiology of erectogenesis and the pathophysiology of ED has resulted in the development of effective therapies with different modes of application: intracavernosal injections, intraurethral administration, and oral therapies. The launch of the first oral agent (sildenafil) in 1998, a decade ago, has not only increased the awareness and acceptance of ED as a treatable condition but has also resulted in the diagnosis and treatment of ED by primary care physicians, where previously it had been the domain of the urological specialist. Thus, it is important that not only the urologist but also the general practitioner should be familiar with the interpretation of clinical trials for ED so that they are able to make informed decisions in treatment planning and in offering the appropriate therapy.

Although the market for products to treat ED has now been established, there are various agents in development, both oral and other (e.g. nasal, inhaled or intracavernosal). Regulatory approval is based on the indication and need for the drug, the therapeutic outcomes, and the adverse events profile. For non-life-threatening conditions such as ED, the risk–benefit profile of the drug is important, especially for patients with or receiving medication for cardiovascular disease. This chapter seeks to outline the current acceptable methodologies for ED clinical trials and also to provide guidance on the evaluation of data for these trials.

Rationale and design of clinical trials

Development of drugs for ED, or indeed any indication, requires a carefully phased and progressive approach. Each phase of the drug trials process addresses different and specific areas of investigation or groups of questions, the outcomes of which support subsequent phases. It is essential that clinical trials be conducted in compliance with the most recent standards of Good Clinical Practice (GCP). These standards ensure that the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials are performed to common standards and provide assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

Phase 1 trials

Phase 1 trials are usually conducted in healthy young volunteers and may be followed by the same study performed in older volunteers. As these trials are the first time the drug is administered to humans, it is important that suitable precautions are incorporated into the study design to ensure the safety of the volunteers and subjects. Such trials are usually conducted in a hospital or a clinical research unit where adverse events and any toxicity can be carefully monitored and managed.

The overall objectives of phase 1 trials are the evaluation of tolerability, safety, and pharmacokinetics, and they usually involve single and multiple dose studies.

Dose selection for phase 1 studies is based on the results of preclinical toxicological, toxicokinetic, and safety studies in animals and previous in vitro studies. The initial dose selected (extrapolated to humans) is usually much lower than the no-observed-adverse-effect level (NOAEL) and the toxic dose in animal models. The initial dose is often then escalated (in increments of 2: one-fold, two-fold, four-fold and so on) either using the same group of volunteers or a new cohort, until a maximally tolerated dose is reached, thus establishing a dose range with regard to tolerability.

Safety assessments such as vital signs, electrocardiography, clinical observations, and reported and observed adverse events should be regularly and frequently monitored and recorded throughout these trials. Blood and urine samples are also taken at frequent intervals to study the pharmacokinetics of the drug and its metabolites in humans (including maximum plasma concentration, time to maximum plasma concentration, the average plasma concentration, area under the concentration–time curve, and elimination half-life). It is important that these pharmacokinetic parameters are determined for single and multiple doses of different strengths, but
also other variables that may affect the pharmacokinetics of the drug and its metabolites are examined (e.g. age, dosing with or without food, and frequency of dosing). The metabolic pathway of the drug in humans may also be established during these phase 1 studies, which could be indicative of potential drug interactions or special precautions needed in compromised patients such as those with renal or hepatic impairment.

In phase 1 trials of drugs intended for the treatment of ED, it is often difficult to undertake any preliminary efficacy assessments as these are often distracting (e.g. use of the Rigiscan device with visual sexual stimulation) and may interfere with more critical objectives of this phase, namely the assessment of tolerability, safety, and adverse events.

Thus, on completion of phase 1 the following outcomes should be achieved: the determination of an initial dose range in terms of safety, the pharmacokinetic profile of the drug and its metabolites, and the identification of commonly occurring side-effects.

**Phase 2 trials**

The objectives of phase 2 trials are to characterize the preliminary efficacy of the drug and to evaluate safety further.

These studies are conducted in larger groups (ranging from 25 to several hundred) and in patients with ED. These study populations may also include men in high-risk groups (e.g. those with comorbid hypertension or diabetes) or patients who are ‘treatment-resistant’. Early indications of efficacy and safety in these patient subgroups are useful for decision-making and the planning of phase 3 trials.

Trial designs used in phase 2 are similar in scope to those in phase 3 but have shorter treatment periods and smaller numbers of patients. Crossover designs are more commonly used in this phase since these have the advantages of allowing the patient to act as his own control, giving intra-individual comparison and thus reducing sample size and expenditure (Figure 48.1). A two-stage design may also be incorporated, which provides an early decision-making point in terms of the response level. If the response level is low in the first stage (15–25 patients) then the study may be terminated early, reducing the number of patients exposed to the drug. A high or acceptable response level in the first stage will then justify progression to the second stage in which a further 25 or so patients are recruited.

Assessment of efficacy may involve both objective measures, such as penile tumescence determined by Rigiscan or duration of certain degrees of rigidity, or subjective measures, such as daily diaries, patient-reported outcomes, IIEF, and quality-of-life questionnaires. Shortened versions of these subjective measures may be employed as the outcomes from phase 2 studies do not serve as ‘pivotal’ data and so time and cost can be reduced.

It may also be appropriate to investigate more specific safety issues in small groups of patients such as special populations, drug interactions and selected organ system risks (e.g. cardiovascular, neurological, liver, eye).

During phase 2, it is important to explore a wide range of doses and establish the lowest effective dose and the maximally tolerated dose and doses at which toxicity is apparent, allowing calculations of the potential benefit–risk ratio.

Phase 2 studies are becoming an important decision-making stage in drug development for ED. Early identification of a positive safety profile (in particular in terms of cardiovascular risks) is beneficial since this is becoming an increasingly significant issue with regulatory authorities, especially in the treatment of conditions that are not associated with morbidity. In addition, the safety and efficacy results of phase II studies are indicative of those expected in the larger, more time-consuming and costly phase 3 trials and may be important in deciding whether or not to progress with the drug’s development.

**Phase 3 trials**

The objective of phase 3 trials is to establish the body of evidence, both for efficacy and for safety, that will provide the basis of regulatory approval for the drug.

Phase 3 trials for ED are usually multicenter, randomized, double-blind, and placebo-controlled. The simplest design commonly employs parallel arms of fixed dose in which each patient is exposed to one treatment condition only and inter-group comparisons are made at various time points (Figure 48.2). Efficacy may be assessed by analysis of inter-group differences following treatment or change relative to baseline. The duration of such trials is usually 12 weeks, which is deemed sufficient time to predict efficacy over a reasonable
Figure 48.2  Parallel arm design commonly used in phase 3 erectile dysfunction (ED) trials.

dosing period and not so long as to result in excessive drop-out of placebo patients.

Crossover designs may also be used, with the advantage of reducing patient variability, although this may result in a bias towards a positive outcome and be insufficient as a basis for regulatory approval. With the crossover design, consideration should also be given during the planning and analysis of the data to carry-over effects or sequence effects between treatment phases.

There should be a baseline assessment period prior to randomization, during which baseline measures are obtained and patients can be screened and their eligibility assessed. Baseline periods are usually treatment-free but could include single-blind placebo treatment to determine potential patient compliance or to identify patients who are most susceptible to 'placebo effects'. The controlled treatment period is often followed by an open-label extension (6 months to 2 years) during which longer-term safety data can be collected.

The choice of the primary efficacy end-point (or endpoints) is important for phase 3 trials, and reliable, sensitive, and validated measures that produce suitable data for clear analysis should be used. Recent ED trials have employed a combined end-point consisting of the erectile function (EF) domain of the IIEF and questions 2 and 3 of the Sexual Encounter Profile (SEP) diary (ability to penetrate and ability to maintain erection to completion of intercourse). The use of this end-point has been shown to give reliable, reproducible and comprehensible data that have proved acceptable to regulatory authorities, and it is also sensitive enough to detect small treatment effects.

Regulatory authorities may also require that any specific or potential safety issues are addressed at this stage, such as special patient populations and drug interactions, especially since tolerance of any risk associated with ED drugs is low. Many men with ED are middle-aged and have comorbid conditions for which they take concomitant medications. There are two categories of drug interaction that should be considered: pharmacokinetic and pharmacodynamic drug interactions. Pharmacokinetic drug interactions are those in which a concomitant medication may affect the bodily exposure to the investigational drug. For example, inhibition of the metabolic pathway of the ED drug by a concomitant drug would result in raised serum levels of active metabolites, thus potentiating the effect of the ED drug (e.g. inhibition of a cytochrome P450 liver isoenzyme that may be critical to a drug's elimination). Pharmacodynamic drug interactions are unrelated to the pharmacokinetic interactions but are those in which the combined physiological effect may produce a clinically meaningful event, such as lowering of blood pressure or increase in heart rate. For investigation of both of these types of drug interactions, the end-points will be pharmacodynamic, such as vital signs, effects on cognitive function and sedation, or more specific measures such as prolongation of the corrected QT interval, QT dispersion, and shape of the T wave on electrocardiogram.

Special population studies may also be relevant in phase 3, again considering that ED patients tend to be older and to have comorbid conditions (e.g. diabetes, cardiovascular disease), may have impaired renal or hepatic function, may have undergone prostatectomy or pelvic radiation therapy, or may have spinal cord injury, multiple sclerosis or depression. It should be noted that special population studies are often powered to assess safety rather than efficacy.

Phase 4 studies
Phase 4 studies are those conducted after approval, when the drug has been marketed, they may be requested by regulatory bodies or performed voluntarily. The reasons for undertaking these trials are various and diverse. They afford the opportunity to assess longer-term safety, to address specific safety issues that did not prevent approval, and to assess further efficacy and safety in patient subgroups or special populations.

Comparator trials of efficacy with competitor products already on the market may also be conducted and may provide useful data for marketing claims. Similarly, studies that address health economic issues (e.g. overall drug benefit or comparative costs) or quality-of-life issues may provide supportive marketing information. Marketing studies should be conducted and analyzed with the same rigor as the pivotal phase 3 studies.

Selection of study populations
As previously mentioned, phase 1 trials are conducted in small numbers of healthy volunteers. For all other phases in which patients with ED are studied, and especially in phase 3, the
The selection of the study population is of utmost importance since this will determine the value of the data.

The study population should be representative of the overall patient population for whom the drug is intended. This will allow prediction of the utility of the drug in ‘real life’ once marketed, and is of particular importance for ‘pivotal’ phase 3 trials. It is also important for the purpose of these trials that ED is well defined and characterized so that the data can be easily interpreted by both the regulatory authorities and prescribing physicians in the future.

Patients with various degrees of ED severity should be included. Based on the data from the Massachusetts Male Aging Study (MMAS),2 two-thirds of ED patients in the USA with erectile failure have moderate or severe ED. Disease severity is usually categorized using the EF domain of the IIEF, which has a score range of 6 to 30. A score of <10 indicates severe ED, 10–16 moderate ED, 17–24 mild ED and ≥25 no ED. Although it may be considered that those with severe ED may be more treatment-resistant and those with milder disease may only have a small or modest response to the drug, these patient groups are representative of the general population and should be included even though clear demonstration of efficacy with these patients may be more difficult.

The incidence of comorbidities in the general population should be represented in the ED study population (e.g. diabetes, coronary artery disease, hypertension, hyperlipidemia, and tobacco use). In the MMAS, the incidence of hypertension was 33%, of coronary artery disease 16%, and of diabetes 9%, and previously most large-scale trials have recruited such representative populations. However, the incidence of comorbidities does not give an indication of their nature of severity (e.g. the type of diabetes or the presence of diabetic complications).

In defining patient populations, disease etiologies should also be considered. Many patients with ED have comorbidities or predisposing factors that are contributory to the etiology of their disease (e.g. diabetes, hypertension, hyperlipidemia, atherosclerosis, tobacco use, genitourinary disorders, neurological disorders, endocrinopathies, depression) or they may have ED of a psychogenic etiology. However, many of these conditions often co-exist, and classifying etiology as ‘organic’, ‘psychogenic’, or ‘mixed’ can create unrealistic subgroups that may confound the interpretation of the results. Additionally, the assignment of etiology from the patient’s history without investigation (nocturnal penile tumescence or vascular studies) may also contribute to ambiguity in such classifications.

Patients in ‘special populations’ (e.g. post-prostatectomy patients, spinal cord injury patients, men with more severe ED, patients in whom other therapies have failed) should also be studied in smaller trials, which may provide useful results that support the larger ‘pivotal’ trials.

The selection of the ‘representative’ study population is achieved by careful consideration and balancing of inclusion and exclusion criteria. However, patients whose health may be compromised by the study drug or by participation in sexual activity should not be included, although the exclusion criteria should not be so stringent as to restrict patient recruitment to the study.

### Inclusion and exclusion criteria

In phase 3, studies are usually conducted in ED patients, and inclusion criteria generally capture patients who are 18 years of age or older (there is usually no upper age limit), heterosexual, and in a stable monogamous relationship with a partner who is willing to support participation in the trial. Men must specifically complain of ED, which is defined as ‘a consistent difficulty in achieving and/or maintaining an erection sufficient for sexual intercourse’, and their ‘dysfunction’ should have a negative impact on their satisfaction or enjoyment of the overall sexual experience. Their ED should be a consistent rather than a transient problem and it is generally accepted that it should be of a minimum of 3 months’ duration. Some trials include a ‘run-in’ period during which baseline ED can be assessed (rather than relying on patient history) and patients whose ED is not significant in terms of being consistent (e.g. >75% of attempts) can be excluded at this stage. Commonly employed exclusion criteria for recent trials in ED are shown in Table 48.1.

#### Table 48.1 Typical exclusion criteria employed in erectile dysfunction trials

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with penile deformities (e.g. Peyronie’s disease) or penile implants</td>
<td>Patients with priapism (e.g. sickle cell disease, blood dyscrasias, multiple myeloma)</td>
</tr>
<tr>
<td>Patients with predispositions to priapism (e.g. sickle cell disease, blood dyscrasias, multiple myeloma)</td>
<td>Patients with untreated hypogonadism</td>
</tr>
<tr>
<td>Patients with untreated hypogonadism</td>
<td>Patients with untreated diabetes (elevated glycosylated hemoglobin levels)</td>
</tr>
<tr>
<td>Patients with untreated diabetes (elevated glycosylated hemoglobin levels)</td>
<td>Patients with significant baseline liver dysfunction (baseline aspartate aminotransferase or alanine aminotransferase levels &gt; three times the upper limit of normal)</td>
</tr>
<tr>
<td>Patients with significant baseline liver dysfunction (baseline aspartate aminotransferase or alanine aminotransferase levels &gt; three times the upper limit of normal)</td>
<td>Patients with significant baseline renal dysfunction (serum creatinine values &lt;2.5mg/dl or those on dialysis or post renal transplant)</td>
</tr>
<tr>
<td>Patients with significant baseline renal dysfunction (serum creatinine values &lt;2.5mg/dl or those on dialysis or post renal transplant)</td>
<td>Patients with a history of HIV infection</td>
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<tr>
<td>Patients with a history of HIV infection</td>
<td>Patients with drug, alcohol, or substance abuse within 6 months of study initiation</td>
</tr>
<tr>
<td>Patients with drug, alcohol, or substance abuse within 6 months of study initiation</td>
<td>Patients who have participated in another study for the treatment of ED within 30 days of study initiation</td>
</tr>
<tr>
<td>Patients who have participated in another study for the treatment of ED within 30 days of study initiation</td>
<td>Patients who have partners who are nursing or pregnant or who wish to become pregnant during the course of the study</td>
</tr>
<tr>
<td>Patients who have partners who are nursing or pregnant or who wish to become pregnant during the course of the study</td>
<td>Patients who are unable to provide informed consent</td>
</tr>
<tr>
<td>Patients who are unable to provide informed consent</td>
<td>Patients with uncontrolled psychiatric disorders, such as psychosis, manic depressive disorders, or chronic depression</td>
</tr>
<tr>
<td>Patients with uncontrolled psychiatric disorders, such as psychosis, manic depressive disorders, or chronic depression</td>
<td>Patients for whom sexual activity may put them at risk of a cardiovascular event, such as those with:</td>
</tr>
<tr>
<td>Patients for whom sexual activity may put them at risk of a cardiovascular event, such as those with:</td>
<td>• unstable angina</td>
</tr>
<tr>
<td>• unstable angina</td>
<td>• uncontrolled hypertension (systolic pressure &gt;170mmHg or diastolic pressure &lt;100mmHg)</td>
</tr>
<tr>
<td>• uncontrolled hypertension (systolic pressure &gt;170mmHg or diastolic pressure &lt;100mmHg)</td>
<td>• a history of myocardial infarction, life-threatening cardiac arrhythmias, or stroke (within 6 months of study initiation)</td>
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</table>
It is also important to consider the contraindications for drugs of a similar class or mode of action as the investigational agent (e.g. the exclusion of patients using nitrate therapy in trials of a phosphodiesterase type 5 inhibitor).

Outcome assessments

Currently the primary end-points of most ED trials are patient-reported outcomes of sexual function. This represents a shift from the development of earlier ED drugs, for which objective or ‘physiological’ outcomes were used as primary end-points.

Physiological measures

Physiological measures continue to have a role in phase 2, proof-of-concept studies, in which the pharmacodynamic effect of the drug is established. The blood flow through the cavernosal arteries can be assessed using ultrasonography, but the most commonly used method is the Rigiscan device (Timm Medical Technologies) which measures radial rigidity of the penis via two loops placed at the base and tip of the penile shaft and is used with visual sexual stimulation. Tests of this nature do have limitations in that they are intrusive and ‘artificial’ and there is also some contention as to whether radial rigidity is indicative of the axial rigidity required for intromission. There may also be some difficulty in defining clinically meaningful rigidity (and duration of erection), though it is generally accepted that a 55% rigidity at the base (as measured with Rigiscan) is sufficient for intercourse. Although this and other methods of penile plethysmography may be considered to have their drawbacks, they do provide objective measurements of tumescence and data that may be used to support other outcome variables.

Patient-reported outcome measures

The most commonly used measures are self-administered questionnaires (e.g. IIEF) and patient diaries (e.g. SEP). Other patient-reported response variables include structured interviews, global questions regarding symptom improvement, and quality-of-life questionnaires.

The IIEF is currently the ‘gold standard’ in ED clinical trials, since it has been extensively validated and has been found to be reliable, responsive (in terms of sensitivity and specificity), easy to use, and has been translated and re-validated in many languages. The IIEF consists of 15 questions and assesses sexual function in five domains (erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction). The EF domain score (maximum score 30 points) is a commonly used primary end-point, although some trials have used questions 3 and 4 of the EF domain (maintenance of erection on penetration and maintenance of erection to completion of intercourse) as stand-alone primary end-points. The IIEF may also be used to stratify patients according to their baseline severity of ED and then demonstrate change within these groups. Drawbacks of the questionnaire are that it is retrospective (relating to the previous 4-week time period) and that it may be difficult to interpret the clinical relevance of very small point changes from baseline scores for individual domains. It is also interesting to note that although so widely used as a trial end-point, the IIEF has only been validated for use with all 15 questions and not just the two items of the EF domain.

An abridged version of the IIEF questionnaire (consisting of five items) has been developed (the Sexual Health Inventory for Men) to allow for more rapid diagnosis of ED and assignment of severity.

Patient diaries (per-event questionnaires) are used to complement retrospective questionnaires and have been widely used in phase 3 trials. The SEP is one such six-item instrument; it has undergone some validation and shows a good degree of correlation with regard to the erection and intercourse satisfaction ratings with the measures of the IIEF.

Quality-of-life questionnaires have been used as secondary end-points, but because most of these generalized instruments tend to address patients whose health is more compromised than that of the ED patient (e.g. those with cognitive and physical impairment), the results have not been regarded as important by regulatory authorities. However, more disease-specific quality-of-life questionnaires have been devised and, although they continue to be used as secondary end-points, the outcomes may provide support for long-term risk–benefit evaluation.

Safety assessments

Safety evaluation and monitoring of clinical adverse events is fundamental and routine in ED clinical trials and should be conducted in the ‘per-protocol’ population and include data from placebo-treated patients. It should also be noted that in most trials, the size of the patient population is selected to demonstrate efficacy end-points and thus may be underpowered to assess reliably the frequency of side-effects.

Two methodologies for collecting adverse events data are commonly used: symptom checklists and structured interviews. The use of specific questions (checklists) to prompt the reporting of particular or expected adverse events is not used in phase 3 and more ‘open’ questions are commonly employed. Symptom checklists have the advantage of standardizing reporting within and between trials, but the structured interview will allow for the recording of unexpected adverse events.

Data may be reported as either per-patient incidence or per administration. The per-patient incidence has been widely used in most previous ED trials and is useful in giving an indication of the probability of a patient experiencing that side-effect, whereas the per-administration incidence will indicate whether the adverse event consistently occurs. Adverse events are reported as mild, moderate, or severe, and they are also classified as being possibly, probably, or definitely related to the study medication. Such classification of causality is assigned by the study investigator and as such is subjective in nature; thus care should be taken in the comparison of adverse events profiles from different trials.

Controlled trials of 1–2 years’ duration and long-term follow-up in phase 4 provide invaluable evidence for the overall clinical adverse events profile of a drug. The occurrence
of a low incidence of adverse events that are medically significant should also be considered as these may only be apparent in studies of large sample size. Alternatively, it may be appropriate to conduct trials designed to address specific safety issues, such as the drug’s effect on cardiovascular parameters, vision, and cognitive functioning, or drug interactions.

### Data analysis and statistical considerations

It is important that a biostatistician is consulted both in the design and data analysis of clinical trials in ED (in particular phase 3 trials). Such an expert can advise on issues such as

| Table 48.2 Guidance notes for the interpretation of clinical trials in ED |
| --- | --- |
| **Trial design** | Crossover design | Patient acts as own control giving low patient variability. There may be a potential carry-over effect of treatment to the next study phase. This design may lead to a bias towards positive outcomes. |
| **Baseline measures** | A no-treatment, run-in phase allows determination of baseline severity of ED. |
| **Single-blind, run-in** | A run-in including single-blind, non-active treatment allows for indication of treatment compliance and screening for patients susceptible to placebo response. |
| **Duration** | Most phase 3 ED trials are a minimum of 8 weeks’ treatment – most often 12 weeks. |
| **Age** | A patient population with a mean age of >50 years may lead to overestimation of efficacy and underestimation of adverse events and hemodynamic effects. |
| **‘Responders’** | Including ‘responders’ (especially to agents of the same therapeutic class) may exclude patients with more severe ED and not be representative of the general population. |
| **Ethnicity** | Most ED trials to date have enrolled 85% white patients. Care should be taken in extrapolating such data to other ethnic populations (e.g. Black, Asian, Hispanic). |
| **Baseline severity** | A study population with two-thirds of patients having moderate-to-severe ED is thought to be representative of the general population. Data from trials in patients with lesser baseline ED severity should be interpreted with caution. |
| **Etiology** | If etiology of a patient’s ED has been assigned by history and physical examination, without further investigations, then such diagnoses and assignment of etiology may not be accurate. |
| **Comorbidities** | The incidence of comorbidities (e.g. diabetes, coronary artery disease, hypertension, hyperlipidemia and tobacco use) in a study population should be similar to that of the general population. Incidence of comorbidities should be used only as a general comparison since it does not give information on the severity of the comorbidity. |
| **End-points** | Primary | Primary end-points should be assessed at baseline, during treatment, and at the end of treatment. The EF domain of the IIEF and the SEP event log (questions 3 and 4) are the most widely used primary end-points. |
| **Secondary** | Global questions of efficacy and quality-of-life questionnaires tend to be used as secondary end-points. |
| **Physiological Methods** | Objective measures of tumescence (e.g. Rigiscan) are more commonly used as end-points in phase 2 trials. |
| **Patient population** | Symptom checklist allows standardized reporting within and across trials. Open questioning allows information on unexpected side-effects to be captured. Patient numbers for most phase 3 trials are selected to demonstrate efficacy end-points and may be underpowered to assess frequency of side effects reliably. Safety analyses should be conducted in the ‘per-protocol’ population to capture withdrawals due to adverse events. The side-effect profile in placebo-treated patients should also be presented for comparison. |
| **Incidence of adverse events** | Data are usually presented as per-patient incidence, which indicates the probability of a patient experiencing the side effect. However, this does not give an indication of the consistency of the side-effect (e.g. whether it is likely to occur with every administration). |
| **Severity and causality** | Adverse events are usually described as being possibly, probably, or definitely related to the investigational agent. These categories are usually investigator-assigned and caution should be exercised when making inter-trial or inter-agent comparisons. |

ED, erectile dysfunction; EF, erectile function; IIEF, International Index of Erectile Function; SEP, Sexual Encounter Profile.
sample size and power, the statistical model, the optimum
design to employ (having considered the trial objectives), and
whether the use of covariate analyses might be appropriate.

For analysis of efficacy outcomes, the intention-to-treat
(ITT) population should be considered – that is, data from all
randomized patients should be included. If the data from only
those patients completing the study are analyzed, then a bias
in results may be induced. However, the ITT principle should
not be applied to the analysis of adverse events, where
withdrawal from the study may have been due to side-effects
or an adverse event.

The magnitude of treatment effect in ED trials may be
described using various measures, such as the group mean
change from baseline or the percentage of responders in active
versus control groups. Use of the latter requires prior definition
of a ‘responder’, and there are currently no widely agreed
defining criteria of an ED responder. The definition of a
responder is also confounded by the fact that no normative
data exist for what is considered ‘acceptable’ sexual performance
in differing age groups. Thus, since this measure is not
standardized it is preferable to use several measures of efficacy,
including quantitative measures (e.g. number of successful
attempts of intercourse) and qualitative measures (e.g. global
satisfaction).

The use of covariate analyses may be appropriate when dif-
fferences in baseline characteristics of study groups exist. Such
analyses include the degree of ED, age, duration of ED, and
other demographic characteristics.

Interpretation of clinical trials

Interpretation of clinical trials for ED requires careful consider-
ation of study design, study populations and enrolment,
efficacy end-points and side-effect profiles. Although it is
tempting to compare outcomes of different trials, only the
data from head-to-head comparator trials should be consid-
ered meaningful. Some of the key points that should be con-
sidered when evaluating the results of a clinical trial in ED are
shown in Table 48.2.

REFERENCES

1. Saigal CS, Wessells H, Pace J, Schonla M, Wilt TJ. Predictors and
   prevalence of erectile dysfunction in a racially diverse population.
   Arch Intern Med 2006; 166: 207–12.
2. Rosen RC, Cappelleri JC, Smith MD, Lipsky J, Pena BM. Develop-
   ment and evaluation of an abridged, 5-item version of the Interna-
   tional Index of Erectile Function (IIEF-5) as a diagnostic tool for
   between self-reported erectile dysfunction and erectile dysfunc-
tion as defined by five-item international index of erectile
   function in Taiwanese men older than 40 years. Urology 2007; 69:
   743–7.
4. Simon R. Optimal two-stage designs for phase II clinical trials.
   Erectile Function (IIEF): a multidimensional scale for assessment of
6. Wyllie MG. Clinical trials for aspiring dummies (and urologists).
7. Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB.
   Impotence and its medical and psychosocial correlates: results of
   forces vs Rigiscan radial rigidity as a function of intracavernosal
   pressure: why Rigiscan does not predict functional erections in indivi-
Sexual function in congenital anomalies

CRJ Woodhouse

Introduction

All of the problems that are commonly seen in an andrology clinic may be the result of the major congenital genitourinary anomalies (Table 49.1). Surprisingly, most of those affected have a rather better sex life than might be expected. Furthermore, the recent advances in the management of male infertility will be of particular benefit to those whose testes are normal but whose ejaculatory function is compromised by their anomaly or its reconstruction.

Gross as some of these abnormalities are, very few commonly cause erectile failure. The main exception is severe myelomeningocele. General sexual function may be compromised for six possible reasons.

1. The penis may be grossly malformed (e.g. extrophy, micropenis).
2. The penis may be a little deformed but the patient’s perception may exaggerate the deformity that sexual function is impaired (e.g. hypospadias).
3. Obstructive lesions of the bladder outlet may cause back pressure on the prostate, leading to ejaculatory failure and seminal abnormalities (e.g. posterior urethral valves).
4. Developmental failure may impair hormonal or ejaculatory function (e.g. prune belly syndrome).
5. Penile innervation may be incomplete (e.g. spina bifida) or destroyed by pelvic surgery.
6. Embarrassment about some aspect of the general abnormalities may prevent the formation of a partnership in which intercourse can take place (e.g. an external urinary diversion).

Whatever the anomaly, it should always be assumed that erectile function and intercourse are desired and possible until proved otherwise. It is astonishing how severe handicaps can be overcome and how small a penis is necessary for apparently satisfactory intercourse.

Penile malformations

Exstrophy and epispadias

Reconstructive surgery of the basic bladder problems of the exstrophy–epispadias complex has progressed so much that patients can now live a normal life and, in the past 20 years, can expect to have a normally working bladder. Although it has always been recognized that the penis required reconstruction as well, a good functional result for sexual intercourse was not always achieved. The exstrophy patient now grows up in normal society and has the same sexual and reproductive aspirations as his peers. My clinical impression is that their libido is as high as that of other adolescents. It is a matter of priority to reconstruct the genitalia to allow normal intercourse to take place. (In this section, the terms ‘exstrophy penis’, and ‘exstrophy pelvis’ encompass the same anomalies in epispadiac patients.)

Genital anatomy in exstrophy

The anatomy of the exstrophy pelvis and penis is obviously abnormal, the details of which have been investigated clinically, by cavernosography, computerized tomography (CT), and magnetic resonance imaging (MRI), by experimental models and by dissection.¹

The visible part of the penis (Figure 49.1) is short – not, as might be thought, because most of the penis is buried in the perineum. However, the penis is longer if the divarication of the pubic bones is 3cm or less and it is shorter if the divarication is 4cm or more.² In the past, surgical apposition of the pubic bones was said not to lengthen the visible penis. Some evidence suggests that the visible penis is longer if the pelvic ring is closed.³ Osteotomies performed in infancy may be more effective in producing a normal penis, at least in childhood.

MRI investigation of the normal and the exstrophy penis has established that, whatever the condition of the pelvic ring, the exstrophy penis is short but broad. The total corporeal length was 60% greater in normal subjects (16.1cm, versus 10.1cm in exstrophy).⁴ Most of this deficiency was in the anterior or exophytic part of the penis (12.3cm for normal subjects versus 6.9cm for exstrophy). The posterior penis was much the same length in both (3.9cm versus 3.2cm). The corporeal diameter was 1.0cm in normal men and 1.4cm in exstrophy men. The abnormalities may be exaggerated by the recession of the supra pubic area (Figure 49.2), absence of the mons pubis, and the normal size of the scrotum.

The prostate is present. In the initial dissection in the neonate it is detached from the penile urethra and remains in its normal relationship to the bladder base. In adult men
the prostate is of normal weight for age but lies completely behind the urethra. The veru montanum (which is normally positioned) is a useful landmark for surgery in later life.

The shape of the erect penis depends on the initial reconstruction. In the natural state, the erect epispadiac penis has a tight dorsal chordee (Figure 49.3). Cavernosography in these cases shows that the site of the maximum curvature is at the point where the corpora emerge from the perineum. The degree of chordee is variable. In some the angle is such that sexual intercourse is possible either in the conventional position or in one that brings the female introitus in more direct apposition to the penis.

A more complex deformity occurs when one or both of the corpora are damaged in the initial surgery so that they fail to fill completely. If one corpus fails to fill on erection it acts as a ‘bow-string’ on the other and causes lateral deviation in addition to the dorsal chordee (Figure 49.4). If both corpora are

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**Table 49.1 Literature review of sexual function in men with a small penis.**

<table>
<thead>
<tr>
<th></th>
<th>Reilly and Woodhouse²⁴</th>
<th>Miller and Grant²⁵</th>
<th>Money et al.²²</th>
<th>Husmann²⁶</th>
<th>Wisniewski et al.²³</th>
<th>Bin-Abbas et al.²⁵</th>
<th>Van Seters and Slob²⁸</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>20</td>
<td>19</td>
<td>9</td>
<td>20</td>
<td>13</td>
<td>8</td>
<td>3</td>
<td>92</td>
</tr>
<tr>
<td>Gender identity disorder</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2%</td>
</tr>
<tr>
<td>Erections</td>
<td>20</td>
<td>15</td>
<td>9</td>
<td>20</td>
<td>13</td>
<td>3</td>
<td>95%</td>
<td></td>
</tr>
<tr>
<td>Heterosexual</td>
<td>20</td>
<td>6</td>
<td>19</td>
<td>10</td>
<td>3</td>
<td>3</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Homosexual</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Bisexual</td>
<td>15</td>
<td>6</td>
<td>12</td>
<td>6</td>
<td>3</td>
<td>60%</td>
<td>60%</td>
<td></td>
</tr>
<tr>
<td>Regular sexual intercourse</td>
<td>6</td>
<td>9</td>
<td>5</td>
<td>6</td>
<td>0</td>
<td>35%</td>
<td>35%</td>
<td></td>
</tr>
<tr>
<td>Psychological problems</td>
<td>6</td>
<td>9</td>
<td>5</td>
<td>6</td>
<td>0</td>
<td></td>
<td>35%</td>
<td></td>
</tr>
</tbody>
</table>

Blank entries indicate that there were no specific data in the paper.
rudimentary, the visible or exophytic part of the penis is normal except that it is a little higher than usual on the abdomen (Figure 49.5). On cavernosography the corpora appear to have no attachment to the pubic rami. Erection is very limited and the penis unstable. In one of my patients the whole of one corpus and the exophytic part of the other is missing so that there is no visible penis at all. The evidence suggests that the corpora are of equal size at birth and are damaged at the primary (and revision) reconstructive surgery.8

Awareness of the erectile problems and appropriate reconstruction in infancy may improve the function in adults. The techniques for children reviewed by Snyder do produce a short but normal penis with a normal angle of erection.7 Indeed, Perovic et al. have reported that the penis in infants is similar in length to that of normal boys although slightly different in appearance (see Figure 49.3). Even in adolescents and adults correction of chordee can be successful and will give a little increase in length.9

In adult exstrophy patients, the pubic area is nearly always recessed from the uncorrected divarication of the pubic bones. The pubic hair lies on either side of the midline (Figure 49.6). Many exstrophy patients find the appearance distressing and try to hide it from their partner. It is most important, either in infancy or in adolescence, to rotate hair-bearing flaps of skin and fat to cover the midline defect.

Sexual function

There is no reason, special to exstrophy, why the erections should not be normal. Even where both corpora are rudimentary, penile tumescence occurs. Exstrophy patients presenting with impotence should be investigated in the same manner as other males. The only difference is that there is no cross-circulation between the corpora. Therefore, if intra-corporeal prostaglandin is to be used, each corpus will have to be injected individually. Occasional boys appear to have suffered damage to the erectile nerves during pelvic dissection and report lifelong inadequate or absent erections. They respond to small doses of standard medication such as sildenafil.

Much the commonest problem, however, is fear of rejection by a partner because of the obvious penile anomalies. Unfortunately, there is no easy solution. In my experience, the most important part of management is not to raise false
expectations from surgery. Chordee and other erectile deformities can be corrected but there is no surgical means of producing the long, normal penis for which they hope. It is better to use knowledgeable and sympathetic counseling to help the adolescent establish a durable relationship in which normal sex takes place. Boys with extrophy are unlikely to be successful with 'one-night stands', though patients reported by Ben-Chaim et al. were said to have random and short-term relationships.¹⁰

Orgasm is normal. About 75% of men with extrophy will have some ejaculation, occasionally as much as 5ml. Although poor or absent ejaculation may follow genital reconstruction, complete absence of ejaculation is rare but the emission that does occur may be slow and may continue over several hours after orgasm. Some patients describe a more or less continuous urethral discharge of semen-like fluid.⁶,¹¹,¹²

It has been suggested that patients who had early urinary diversion have better ejaculation than those who have been reconstructed (particularly if the reconstruction was unsuccessful). Most authors who have specifically addressed the point have results that appear to support this conclusion. Evidence from the literature as a whole is inconclusive. In several papers it is difficult to work out which patients were diverted and which were not, or whether the ejaculation was anything like normal.¹³

With or without surgical correction, the men appear to have a normal libido. They form stable partnerships with normal girls and have normal family life. Hensle reported that 60 of 77 adult males were cohabiting with a sexual partner and a further 8 had a regular sexual relationship (personal communication). About a half of men who are trying to will be able to father a child.¹⁴

Cloacal extrophy

Cloacal extrophy is a very rare and extreme form of extrophy involving the intestinal tract as well as the bladder and genitalia. Many patients have an associated spina bifida as well. There were no reported survivors before 1960. The early survivors now are reaching adulthood and the limited data on long-term outcomes are fuelling much ethical debate at present.

Initially, standard advice was that 46,XY infants should be re-assigned as female. Cases have been cited where refusal of such advice by the parents has resulted in poorly adjusted adolescents who commit sexual offences. In a series of eight males with cloacal extrophy only one achieved successful vaginal intercourse. Two were impotent and three required intensive psychiatric counseling.¹⁵ About two-thirds of pediatric urologists still accept this recommendation.¹⁶ However, recently there has been a reaction against this policy because of the observation that at least a third of children who had been re-assigned as female subsequently re-adopted the male sex.¹⁷ Some are living as successful males and there has been at least one reported pregnancy. Psychological reviews suggest that the broad problems of cloacal extrophy are more important than the single issue of sexual function.¹⁸

The small penis

It is generally agreed that a small penis must have normal anatomy but be more than 2.0 or 2.5 standard deviations below the normal stretched length. Thus it ranges from 1.75cm to 2.7cm at birth.¹⁹,²⁰ Growth curves have been constructed from which the normal penile lengths can be derived at any age.²¹ The andrologist may be asked to see a neonate or adult with a small penis for whom endocrine treatment is impossible or has failed. The questions that then arise are what use will the present organ be, can it be made any bigger and, in an extreme case, should a sex re-assignment be made?

Sexual function with a small penis

There is now a considerable literature on sexual function in men with a small penis (Table 49.1). At first sight, it may appear to be self-contradictory. However, there is a strong selection bias. Papers derived from psychology units inevitably describe a high incidence of psychological problems²²,²³ but those that come from more general clinics give a picture of male sexual behavior that is close to normal.²⁴-²⁶ The most striking features of all series are the strength of male gender identity (98%) and a potency rate of 95%. Not surprisingly, the two reported cases of gender identity disorder were from a psychology unit.

In the 20 adults reported by Reilly and Woodhouse, all had heterosexual interests, erections, and orgasms, and 11 of 12 had ejaculates. The mean age of sexual debut was 16.4 years (range 13.5–20) while the normal is 16.2. All claimed to find intercourse enjoyable though their partners' views were unknown. One patient had a wife and a mistress. The partnerships were stable and long-lasting, a situation that some patients attributed to the extra attention that had to be paid to intercourse because of the short penis. Although vaginal penetration was usual, there was an experimental attitude to positions and methods. One patient was the father of a child.²⁴

It seems safe to conclude that even the possession of the very small penis illustrated in Figure 49.7 is compatible with a normal male role, especially with proper parental support. The finding of a micropenis at birth should not, on its own, be grounds for re-assignment to female.

Hypospadias

There are few major subjects in urology that are so difficult to review than the adult sexual consequences of hypospadias. Data on adults who were born with hypospadias are few and often imprecise. Adult patients who now are available for outcomes analysis were operated on in the 1970s. Much of the evidence cited in this chapter comes from surgery that is even older. Techniques have changed and surgical results have improved. However, against this must be set the rise in patient expectations that has come with greater education. Considering the large number of boys who are operated for hypospadias and the small number that present themselves in adult life with complications, it is reasonable to believe that the majority of patients have had a good enough result not to seek revision surgery.

Appearance

There is a wide range of size and appearance of the normal penis. Like other human features there is a variation in that
which is considered normal or beautiful. It has been established, however, that the meatus is not always at the tip of the penis. Thirteen percent of apparently normal men have a hypospadiac meatus and in a further 32% it is in the middle third of the glans. Most of these men thought they were normal, all voided normally and had sexual intercourse. It could, therefore, be said that minor degrees of hypospadias, especially if there is no chordee, do not greatly matter to men or to their partners.

For men who have had surgery for hypospadias, there is often disagreement with the surgeon on the success of the operation. Up to 80% of adolescents are dissatisfied with their penile appearance, though only 38–44% sufficiently so to want further surgery. There is a difference in results depending on the attitude of the community to circumcision: in countries where childhood circumcision is routine, results are perceived to be better than in those where it is uncommon. When there is a direct comparison between the opinions of the patient and the surgeon, there is almost no agreement.

Mureau et al. have introduced the helpful concept of the ‘Genital Perception Score’ (GPS). Eight features of the penis are scored from one to four, giving an overall range of eight to 32 with the highest score being the best result (Table 49.2). This allows a numerical comparison between observers and helps to identify areas of concern for the patient. It is important to note, however, that three of the eight features were concerned with penile size, which cannot be altered by surgery. The authors asked patients and their surgeons to give a GPS for the surgical result. Surgeons gave a mean score of 29.1 and the patients gave a mean of 25.1, a difference that is statistically significant (Figure 49.8a). For the uncorrectable, size-related features, the patients gave a mean satisfaction score of 3.1 (out of 4) while the surgeons gave a score of 3.9. For the features related to the surgical result, the patients’ score was 3.2 and the surgeons’ was 3.5 (Figure 49.8b). Much of the dissatisfaction seems to have been related to the circumcision appearance in a society where circumcision is unusual and is perceived to shorten the penis.

It seems likely, therefore, that surgeons can reliably correct those abnormal features of the hypospadiac penis that are amenable to reconstruction: chordee, the hooded prepuce (especially if the circumcised appearance is acceptable) and the position of the meatus. Features related to the size of the corpora or the glans, are not correctable.

Size may be a cause of dissatisfaction. The hypospadiac penis is often said to be short. In part this may be because of the circumcised appearance, especially in countries where infant circumcision is unusual. However, where a formal measurement has been made, 20% of hypospadiac penises were below the 10th centile. The finding was most marked in the adolescents, with four of seven being below the 10th centile (Figure 49.9). The numbers of patients in each age group, especially the post-pubertal group, were small and the results must be taken with care.

### Chordee

Hypospadias repairs currently in use put great emphasis on correction of chordee, recommending frequent intra-operative artificial erections to check that the penis is straight. Older repairs were much less successful in this regard, and at long-term follow up 20% or more had residual chordee (Figure 49.10). As with strictures, it is very important to confirm that the man actually has significant symptoms from the chordee. The bend may be sufficient to prevent intercourse and therefore demand correction. There is also a group of men for whom the bent appearance, even if not a physical impediment to penetration, is an emotional cause of sexual dysfunction. It is interesting that in Summerlad’s late review, 13 patients were thought, objectively, to have chordee, of whom only 8 had symptoms, while 2 of 47 complained of curvature that was not confirmed on examination. Recent results have been better, with only 18% of men having significant chordee.

Chordee can occur many years after an apparently successful repair, either at the site of the original operation or remote from the site of the hypospadias. In a group of 34 men referred for alleged recurrent chordee, 22 were identified who had

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**Table 49.2 The features of the genital perception score described by Mureau et al.**

<table>
<thead>
<tr>
<th>Correctable features</th>
<th>Uncorrectable features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glans shape</td>
<td>Penile size</td>
</tr>
<tr>
<td>Position of meatus</td>
<td>Penile thickness</td>
</tr>
<tr>
<td>Scars</td>
<td>Glans size</td>
</tr>
<tr>
<td>Scrotum</td>
<td></td>
</tr>
<tr>
<td>General appearance</td>
<td></td>
</tr>
</tbody>
</table>

All the features are scored, but for the purposes of Figure 49.8, they are divided into surgically correctable and uncorrectable items.
adequate initial surgery, confirmed by intra-operative erection and reported absence of chordee during follow-up. All had had proximal, or even penoscrotal, chordee and all had had a tubularized free-graft urethroplasty. The chordee developed during puberty, from 12–18 years of age. The median age of presentation was 21 years and a mean of 17 years after the original surgery. Although in two-thirds of cases, the urethra was shortened and fibrosed, division of the urethra did not correct the chordee in all cases. Disproportion of the corpora was present in 68% of men, with or without short urethra. The cause of this late deterioration is unknown.

Sexual intercourse

Problems, both physical and emotional, with sexual intercourse, have been reported. The 'physical causes' include soft glans, poor ejaculation, tight skin, and pain. 'Emotional causes' are small size, poor appearance, and the anxieties from the physical causes. The difficulties in assessing these claims lie partly in the fact that similar problems are found in many adolescents (with or without genital anomalies) and partly that hypospadiac men appear to have intercourse in much the same way as everybody else. All reported series record that most men have sexual intercourse, even though the quality and quantity may be difficult to decipher from the data. Figures for successful intercourse range from 77% to 90%, . Curiously, frequency of sexual intercourse does not seem to be related to the success of the repair, though it is probably related to the degree of severity of the original hypospadias.

Nowhere in medicine is it more necessary to have control patients than in the assessment of adolescent sexual function. The greatest difficulty lies in the identification of a satisfactory control group to compare with the hypospadiac patient. Without controls it is impossible to know whether the myriad of sexual problems that have been identified are caused by the hypospadias. There is no group that mirrors all of the features of hypospadias, but infant circumcision, herniorrhaphy, and appendicectomy have all been used. Two studies have shown that there was no difference in the number of sexual episodes or their perceived quality between patients with hypospadias and controls (herniorrhaphy patients and circumcision patients, respectively). . This was despite the observation that the patients with hypospadias had significantly more erectile problems, such as curvature, shortness, and pain, than the controls. . There was no significant difference in the ages at which boys started masturbating, necking, or having sexual intercourse. Hypospadiac men described themselves as more sexually inhibited than controls who had had a hernia repair (24% vs 1.8%).

The quality of sexual satisfaction may be different when the hypospadiac man has suffered complications since there is a correlation between more complications, dissatisfaction with the surgical outcome, and dissatisfaction with sexual performance.

Men with major complications in the surgical outcome often have physical difficulty with intercourse. Apart from
Ejaculation

The first, or prostatic, phase of ejaculation is normal in men with hypospadias. The next stage is the expulsion of the semen by the bulbospongious muscle. In proximal hypospadias, this muscle is likely to be absent. It is, therefore, not surprising to find that ejaculation is unsatisfactory in 63% of men with severe hypospadias even though orgasm is normal in most.27 Poor surgical results from the distal urethroplasty may cause a baggy meatus (Figure 49.12) or even a diverticulum, further slowing the ejaculation. The reconstructed meatus lacks the support of corpus spongiosum. Even in the unoperated hypospadiac penis it is apparent that the meatus for some distance proximal to the meatus consists of little more than skin (Figure 49.13). In more general reviews most authors state that ejaculation is normal. However, by asking the right questions, Bracka found that 33% had ‘dribbling ejaculation’ and 4% were dry.30

Figure 49.11 An unsuccessfully reconstructed hypospadiac penis (hypospadiac cripple).

Figure 49.12 Operative photograph of a hypospadias repaired in childhood by the Dennis Brown buried-strip method. Note that the meatus is not terminal and the urethra is baggy.

Figure 49.13 An unoperated penis with glanular hypospadias, showing the deficiency of the spongiosus in the distal urethra.

Psychological aspects of sexual intercourse

Emotional satisfaction with intercourse is particularly difficult to measure, and series without controls are valueless. Most teenagers, exploring their sexuality, have anxieties that are unrelated to any penile abnormality though a penis that is perceived to be abnormal may get the blame. Penile size is a source of considerable anxiety in many adolescents. Limited research is available on the relationship of penile size to sexual satisfaction. Men with micropenis and with epispidias have intercourse that is satisfactory to themselves, though the opinions of their partners have not been investigated (see above). An investigation of women with multiple sexual partners has suggested that intercourse with an uncircumcised penis gives greater pleasure than a circumcised one.41

As there is no realistic means of enlarging the penis in hypospadias, it seems wise to help the patient to make the best use of that which he has, rather than embark on surgery for lengthening, which has a most uncertain outcome. If the comparative trials of Mureau et al.31 and Aho et al.37 are correct, hypospadiac boys are not greatly different from their peers in their sexual activity and enjoyment.

There is conflict over the effect of the success of the repair. Bracka made the interesting observation that those who were
satisfied with the results of their repair had a sexual debut at a mean of 15.6 years old, while those who were dissatisfied had a debut at 19 years old. On the other hand, it has been reported that in a group of boys whose 'curative repair' was delayed beyond 12 years old, 50% had their sexual debut before the definitive surgery. It could be said that the experience of intercourse, acknowledged by the authors to be less satisfactory, drew attention to the shortcomings of the repair.

Fertility
It seems probable that boys with uncomplicated hypospadias are normally fertile. There have been no studies of a large cohort of hypospadiac patients. There is no excess of patients with hypospadias in infertility clinics. In an apparently unselected group of 169 hypospadiac men, 50% were found to have a sperm count below 50 million/ml and 25% had below 20 million. More than half of those with the lowest sperm counts had associated anomalies, such as undescended testes, which might have accounted for the poor result. In a detailed study of 16 hypospadiac men, true oligo-astheno-teratozoospermia was found only in the 2 patients with perineal hypospadias; low counts were seen in 1 of 3 with glanular and in 2 of 6 with penile hypospadias, but other parameters were normal. With two minor exceptions of slightly elevated luteinizing hormone (LH), all the patients had normal hormone profiles.

New adult patients
From time to time a man will present with hypospadias who has had no previous surgery. Most often BXO will have caused a stricture (Figure 49.14). Occasionally, a man will present with an unconnected symptom and the hypospadias will be a chance finding. Even an uncomplicated hypospadiac meatus may not be large enough to accept a conventional cystoscope or resectoscope. The distal urethra is often fragile with no supporting corpus spongiosum and may easily be damaged by instrumentation (see Figure 49.13).

Before deciding on treatment, it is essential to establish what the patient hopes to achieve from surgery. With limited objectives, such as enlargement of the meatus, simple, local surgery will suffice. For complete reconstruction, the same techniques may be used as in children. Unfortunately, the complication rate of around 33% is much higher than that seen in younger patients. Wound healing seems to be slower and the infection rate higher, than in children. BXO should be treated by complete excision of all affected tissue as a first procedure. Reconstruction should be undertaken only when healing is complete, all edema has settled, and it is clear that all BXO tissue has successfully been removed.

Careful discussion with the patient about objectives and possible outcomes is essential. Couples may seek advice on the inheritance of hypospadias. There is an increased risk of hypospadias if the father or one of his first-degree relatives has hypospadias. It is difficult to determine an exact figure since the subject may not be discussed within the family. In a review of 430 patients with hypospadias, 21% had another affected family member. It should also be noted that hypospadias is the most common congenital anomaly in boys conceived by intra-cytoplasmic sperm injection, with a relative risk of 3.0.

Obstruction and disorders of development

Posterior urethral valves
A congenital urethral valve causes obstruction to bladder outflow and, in most boys, some consequent damage to the kidneys. However, the back-pressure also causes dilatation of the prostate (Figure 49.15). Little is known of the consequences of the prostatic damage or other factors on sexual function and fertility. There is a very wide spectrum of severity in boys with posterior urethral valves, ranging from death in utero or in early infancy to such minor symptoms that diagnosis is only made in childhood. There is also a selection bias in patients volunteering to be investigated, since those that are fertile will see little point in providing semen samples.
Work from my own unit has shown that abnormal semen and poor ejaculation occurs in up to 50% of boys. The seminal abnormality is characterized by lack of liquefaction, low sperm count, poor motility, and high pH (up to 9.5). Puri et al. had similar findings except that no patient (out of 5) had oligozoospermia; 4 had abnormal sperm agglutination. Hormone profiles were normal except that 5 of 9 had hyperprolactinaemia, which contributes to slow ejaculation.48,49

The effect on fertility is unknown but up to a third of my patients appear to have some difficulty in achieving paternity. The dilated posterior urethra means that inadequate pressure is established at the beginning of orgasm, resulting in less forceful (or absent) ejaculation.52 Serum prostate-specific antigen has been found to be normal in all of the small number of young men in whom it has been measured.53 Holmdahl and Sillen asked their patients about paternity but did not do any semen analyses.54 They found that 11 of 13 men who were not uremic had produced 18 children between them (one with the help of intra-cytoplasmic sperm injection). None of 6 uremic men were fathers. They concluded that uremia was the cause of infertility.54 Although uremia is certainly a cause of impaired fertility, it does not cause the seminal abnormalities that are well documented.

**Prune belly syndrome**

Prune belly syndrome is a rare syndrome that consists of bilateral undescended testes, absence of muscle in the anterior abdominal wall (which gives it the name), and variable abnormalities of the upper urinary tracts. It is probably due to a mesenchymal developmental defect but could be due to transient urethral obstruction in utero. About a third of babies die in utero or in the first few weeks of life, but the remainder grow up normally, though often with impaired renal function.

In the 1950s and 1960s it was felt that the testes were so abnormal that fertility and malignancy need not be considered. Orchiopexy was, therefore, delayed either until a major reconstruction was performed or until late childhood. It was not surprising, therefore, to find that the testes could just about produce sufficient hormones to maintain masculinity but only at the price of high pituitary drive: serum testosterone levels in adulthood are usually in the normal range but serum LH levels are two or three times normal.52 Men with prune belly syndrome were thought to be inevitably sterile and testicular biopsies showed Sertoli cells only.

It has now become apparent that some germ cells are present and so the outlook is not so bleak. There have been reports of sperm in the semen. There has been at least one pregnancy using intra-cytoplasmic sperm injection and resulting in twins, one of whom was normal though the other had multiple anomalies. There have also been three reported cases of germ cell neoplasia.53–55

**Disorders of perception**

**Impotence in adolescents**

Erectile dysfunction (ED) is rare in adolescents, although the incidence of sexual dysfunction is greater than 50% in some adult populations.38,56 Those adolescents who seek medical attention for sexual dysfunction without neurologic or structural etiology are likely to have a psychological or psychiatric problem. The very fact that the presentation is with impotence is a measure of the seriousness of the underlying condition. Further questioning may reveal that some of these adolescents are simply seeking a prescription for phosphodiesterase type 5 inhibitors such as sildenafil. The fastest growing group of sildenafil users is young men aged 18–45 years.57 Non-psychological causes of ED in adolescents are the same as in adults, including endocrine disorders (diabetes, hyperprolactinemia, hypogonadism), fibrosis caused by priapism in sickle cell disease, and trauma, such as posterior urethral disruption. Management is the same as for adults.

**Disorders of pelvic innervation**

**Myelomeningocele**

Spinal abnormalities, especially myelomeningocele, are probably the only strictly physical cause of congenital erectile failure. Even the most crippled spina bifida patient has sexual desires. Normal sexual intercourse is quite possible even when life is spent in a wheelchair. Those with minimal neurological defect are probably normal. Those who are grossly abnormal are often assumed to be ‘asexual’ though this may be a cover for our unwillingness to tackle a difficult subject. In investigating sexual function, there is a difference between theory and practice and between findings in adolescents and adults. In practice, sexual activity is more common than would be expected from theory or from investigating the adolescent alone.

**Sexual development**

Patients with severe congenital disabilities often fail to develop normal sexuality because of lack of privacy and because of dependence on others for normal daily living. They have low social and sexual confidence. Surprisingly, however, even those who can walk and whose spina bifida is ‘hidden’ also have major sexual problems. They will have uncertain bladder and bowel control, which leads to an unwillingness to mix with their peers on an equal basis. It is most important not to imagine that an apparently minor level of neurological disability means that sexuality is normal.34 The physical aspects of sexual function that depend on the brain are generally intact, while those which depend on the spinal cord will be damaged in line with the neurological level.

When children are brought up in the mainstream of education and integrated in school, the social results are excellent. In a study to compare 11 dimensions of self-image in adolescents with spina bifida with those of their peers, there was no difference in 10. Unfortunately, the 11th was the dimension of sexuality, which was significantly below normal.59

Adolescents with spina bifida are often ignorant of even very straightforward aspects of sexuality that should be taught within the family. The ordinary facts of reproductive life often are not given. It is not surprising, therefore, that
they have very little sexual contact. Dorner interviewed 63 spina bifida teenagers and their families. Seventy percent of the patients had moderate or severe handicap. It was found that sexual discussion with peers was inhibited. Twenty-three percent did not know how babies were conceived. Few patients understood anything of contraception. Only 18 patients had 'dated'.60 This paper was published in 1977. The lack of education in patients who had grown up in the 1960s, a period of great sexual openness and freedom, was worrying enough. Sadly, matters have not greatly improved. In a paper published more than 20 years later, 93% of adolescents expressed a wish to have education in sexual issues but only 39% had received it and only 5% felt that they had adequate knowledge.61

Erection and ejaculation
In assessing sexual potential it is important to remember that erections are often reflex and not necessarily a sexual response. Diamond et al.62 related erections to the neurological defect but pointed out that many observed erections could have been purely reflex in origin. In a series of 52 post-pubertal males, 70% claimed to have erections, in most cases supported by parental observation. Erections occurred in all patients with a positive anocutaneous reflex and in 64% of those with a negative reflex and a sensory level at or below the sympathetic outflow (T10–L2). Only 14% of males with higher lesions and absent reflex had erections.63 With a rather more detailed sexual history, Cass et al. showed that orgasm and ejaculation occurred in 7 of 9 men with a level at L3 or below. Only 3 men with higher levels were studied and, although 2 of them had ejaculations, only 1 had sexual sensation.64

Sexual activity
A recent study from the Netherlands has shown that, in practice, sexual activity in adolescents with spina bifida is limited, especially in those with hydrocephalus (Figure 49.16).65 The situation improves as the patients get older. In a review of 49 adults it was found that 9 had steady partners and 22 were married. Nine had fathered 23 children. Of the others, 10 were under 20 years old, 2 were mentally handicapped, and 2 had over-protective parents. It could, therefore, be said that 88% of those with realistic prospects were married or had a steady partner. Many of the patients were severely handicapped and incontinent, which seemed no bar to their achievements.65

Impotence
Impotence responds to the conventional management, such as intra- corporeal injection.64 Sildenafil may be used with appropriate dose reduction. In the only trial to date in this group, dose escalation was used with patients as their own controls. Eighty percent of men responded to a dose of 50mg. Although one patient subsequently responded to 100mg, it was recommended that such a high dose should not be used in spina bifida. Five of the 11 responders in the series were wheelchair-bound.65,66

Fertility
No figures are available for the overall incidence of infertility in males. However, it is interesting to note that in the study of 49 adults with spina bifida quoted above, 16 men and 15 women were married or had a regular partner. Ninety percent of co-habiting couples had children. Success in partnership and fertility were said to be unrelated to continent or mobility.67

The bigger issue, however, is the risk of the offspring having a neural tube defect (NTD). Combined series have shown an increased risk of NTD to be as high as 4% in the offspring of spina bifida patients. The risk is the same whether the affected parent is male or female, but daughters have a 1 in 13 incidence while the risk for sons is only 1 in 50.65,68

One of the great medical success stories of the past 30 years has been the discovery of the prophylactic role of folic acid. In a double-blind, placebo-controlled trial involving 1195 women with high-risk pregnancy (previous birth of a child with NTD or an affected parent), there were 6 affected fetuses in the treated group versus 21 in the untreated group.69 Even before the discovery of the protective effects of folic acid, the overall incidence had been falling. In a recent study from the UK, it was shown that the incidence of NTD started to fall about 18 years before the use of folic acid began to rise.

Figure 49.16 Histogram to show levels of sexual activity in adolescent males born with spina bifida. Data from Arch Phys Med Rehabil 2005; 86: 979–87.
The incidence fell from about 225 per 100,000 live births to about 48 per 100,000 live births between 1972 and 1990. The number of sales of folic acid was less than 100,000 per year until 1990, rising to 1.2 million per year by 1996.69

However, the main protection against the conception of a baby with an NTD defect is to give the partners of men with spina bifida folic acid 5mg per day for at least 3 months before a planned conception.70 In spite of this prophylaxis, there remains a small risk of an affected pregnancy. At least one cause appears to be an inborn error of folic acid metabolism, which was found in 16 women who gave birth to two successive babies with myelomeningocele in spite of prophylaxis.71

In those with higher lesions, it might be thought that infertility would be due to the impotence. Although this is undoubtedly true in part, a small study has identified another problem. In 10 impotent males with spina bifida, all were found to be azoospermic on analysis of semen obtained by electro-ejaculation. On testicular biopsy, all had Sertoli cells only.72 Poor semen quality has also been reported in men with acquired spinal lesions using electro-ejaculation, especially if ejaculation is infrequent.73

Disorders of sexual development

**Patients raised in the male sex**

The conditions covered by the terms 'intersex' and 'hermaphroditism' have been re-named 'disorders of sexual development' (DSD).73 Infants with any DSD present one of the greatest challenges that the pediatrician can face. In considering the sexual outcome in these and other men with gross genital anomalies, it is important to remember that there is no 'right answer'. Even with the most careful counseling and psychological care, 39% of children have been shown to develop one or more general psychological disorders, regardless of the sex of rearing. Psychological intervention from birth reduces but does not abolish the problem.74

There has been a lack of enthusiasm to raise babies with ambiguous genitalia in the male sex. This has been in part because of the apparent success in raising them as girls, particularly until around 6 years old, and partly because of their poor success as boys. In the 1960s, Money, amongst others, championed the view that even totally normal boys could be raised in the female sex providing the decision was made early enough and constantly reinforced.

At a simple level, lessons can be drawn from babies with abnormal but clearly masculine genitalia. Reference has already been made to classical and to cloacal exstrophy. In the classical form, sexual function as a male has been satisfactory and fertility is possible. However, in a very gross form known as cloacal exstrophy and discussed above, the penis may be so rudimentary that sexual intercourse as a male may be impossible. The genotype is 46,XY and the testes are histologically normal. Even into early adolescence, there has been considerable success in raising the male cloacal exstrophy patients as girls.75 Furthermore, in the small number raised as males, the psychological problems have been overwhelming and there have been reports of criminal behavior. In men with micropenis, there has been a tacit assumption that intercourse as a man would not be satisfactory. As it was easier to create a vagina by surgery than a penis, there was some pressure to re-assign as female. It is not surprising, therefore, that there has been an unwillingness to raise infants with abnormal or ambiguous genitalia as males.

There is now a greater understanding of sexuality. It seems likely that the brain is the main determinant of sexuality. Particularly where the brain has been exposed to androgens in utero, it is most probable that the infant will exhibit male sexual traits. The main exception to this is in complete androgen insensitivity. In this condition, the fetus is 46,XY and the testes are present. However, there are no androgen receptors in the genitalia or in the brain. The phenotype is, therefore, largely female, and androgenization of the brain does not occur. There has also been greater understanding of female sexuality. The vagina is not a passive organ in intercourse but one that is at least as active as the penis.76

Attitudes to sex of rearing have also been influenced by the prospects for fertility. Even very complex problems of infertility can be solved by reproductive technology.

There must be a re-evaluation of previously held truths. Those with DSD must be helped to achieve what is possible with the structures available. It is a mistake to amputate sexually sensitive organs without a definite medical reason. Furthermore, it is naïve to think that female sexuality is so simple that inadequate male genitalia can be ‘cured’ by realignment of sex: there is no evidence to show that the outcome of this policy is satisfactory. Indeed, evidence is emerging to suggest that the outcome is poor: many people with ambiguous genitalia would prefer to keep what they have rather than have bits reconstructed to produce a copy of a specific sex.77

In spite of the theoretical evidence, little is known of the consequences of raising poorly androgenized babies with DSD in the male sex. It is all very well to say that intercourse and even fertility are possible, but quite another to have a ‘normal’ man. Nonetheless, in the absence of a ‘right answer’, the same criteria should be applied to potentially male as to potentially female babies. It is unacceptable to say that a baby will make an unsatisfactory man and therefore it will be raised female.

The question then arises as to whether a proper penis can be made. The early management of any case of DSD is that of the underlying condition. With endocrine correction there may be some growth of the penis. Once the boy has passed puberty further growth of the penis is unlikely. Dihydrotestosterone cream has been used to stimulate penile growth. Both the penis and prostate show rapid growth. In a series of 22 children there was a mean increase in length of 53% in the first month and a further 18% in the second month of treatment. The series included 4 boys who had failed to respond to testosterone treatment.78 Late treatment of a 12-year-old and a 17-year-old boy have been reported, but the responses were poor.79 Until recently, this preparation has been unobtainable in many countries. It is now becoming available again and it may be hoped that further studies on its efficacy will confirm its value.

Surgical enlargement of the penis is limited by the inability to make erectile tissue. It is possible to gain length by releasing the corpora from the pubic bone by dividing the suspensory ligament but at the price of some loss of erectile stability.
If the penis is completely absent, a new penis can be formed from skin flaps using the techniques developed for sex reassignment. Good technical results have been reported in boys with micropenis using both groin flaps and a microsurgical transfer of a forearm flap.\textsuperscript{10,11} The microsurgical technique is claimed to allow return of sensation and even, with time, of erogenous sensation. No attempt was made to insert prostheses for erection and there is no report on the sexual results.

A technique has been described to make a phallus from a skin flap, using the technique for female-to-male sex reassignment, and to ‘piggy-back’ it onto the natural penis. The man then has his own sexual satisfaction from his small natural penis and can penetrate his partner’s vagina with the reconstructed part. The results in patients are reported to be good with very careful selection.\textsuperscript{82,83} In my own very limited experience of the procedure, the appearance is odd and I am doubtful if it can be justified except in those with a very rudimentary natural penis.

As a general rule, a small penis with normal erections should not be sacrificed, but should be used as the basis for sexual function. Every effort should be made to help men to have sexual satisfaction and to end a knowledgeable sexual therapist is invaluable. Surgery on the penis is often poor treatment for problems that lie in the brain. Only if all else fails, and the man is very clear about the likely outcomes, should surgery be done to create a large but sexually insensitive penis.

Adolescent varicocele

Varicoceles are not congenital in origin. However, they have been diagnosed in adolescents for many years. The prevalence data shown in the Table 49.3 go back to 1966. The absence of varicocele before the age of 11 suggests that puberty must play a part in their initiation. By 19 years old, a prevalence of up to 19% makes them common and it might be expected that urology clinics would overburdened with young men complaining of scrotal abnormalities. It would seem to be a rare problem in the UK even now and is seldom seen in general clinics. However, the literature from the rest of the world is full of papers on the subject – at least 20 in 2006 alone.

If varicocele invariably caused significant damage to overall testicular function, the incidence of male factor infertility would be considerably higher than is the case. Abnormalities of tubular histology and function are found more commonly in those with varicoceles compared with controls. As most of testicular bulk comprises the seminiferous tubules, their damage will be reflected in reduced testicular size. If, as has been suggested, the main damaging agent is increased ambient temperature, it is possible that both testes may be affected and so size differential may not be apparent. Ligation of varicocele may reverse the abnormalities and allow catch-up growth of a hypotrophic testis.\textsuperscript{87–90}

In one study of boys between 17 and 19 years of age there was no significant difference in sperm concentration between those who had or did not have a varicocele. Varicocele was associated with reduced motility and an increased number of abnormal forms, which was just significant.\textsuperscript{90} In another study, standard semen analysis showed no difference between boys with and without varicocele, but there was more DNA fragmentation in those with varicocele. DNA fragmentation may be a maker of sperm function, but there is no standard test in clinical use, and the research tests are expensive and difficult.\textsuperscript{91}

In the main, however, abnormalities that have been found in adolescents are related to differences in testicular and varicocele size. Although a definition of significant hypotrophy has been made as a greater than 20% difference in size, two studies from Boston have found no evidence of progression in hypotrophy with sequential follow-up and no correlation with grade of varicocele.\textsuperscript{92,93} However, detailed semen analysis did show significant differences with increasing degree of hypotrophy. Fifty-seven boys at Tanner V were assessed by one or more analyses. Those with >20% reduction in volume had lower concentration and less good motility than those with <20% reduction. Fifty-nine percent of boys had sperm counts of less than 10 million, with 77% having poor motility.

When the volume reduction was less than 20% there was only a trend to impaired semen analysis. With a volume reduction of 10–20%, only 11% had sperm counts <10 million and 67% showed normal motility. With a reduction <10%, none had such low counts and 85% had normal motility. There was no relationship between any of the parameters and the grade of varicocele.\textsuperscript{91}

None of the available tests, including semen analysis, is of value in predicting future fertility. There has been no study comparing operated and non-operated patients with proven fertility as an outcome measure. At present, the most that can be said is that varicocele is associated with structural changes in the testes. Success in treatment may be measured by reversal of these changes.

Varicocele repair has resulted in a significant increase in testicular volumes and consistency. Testicular catch-up growth has been found in 53–90% of adolescents.\textsuperscript{89,95–98} It is noteworthy that when follow-up into adulthood has been possible, the total testicular mass (i.e. the volume of both testes added together) has been the same in operated patients and normal controls and significantly larger than in men newly presenting with varicocele in adulthood.\textsuperscript{96} Studies suggest that varicocele repair in older adolescents significantly increases sperm parameters, especially motility and total motile sperm count.\textsuperscript{92,96,99} Repair probably has positive effects on Leydig cell function by improving serum testosterone level.\textsuperscript{95,96,100}

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<th>Table 49.3 Prevalence of varicocele and associated testicular hypotrophy by age</th>
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<td><strong>Age</strong></td>
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<td>Data from JAMA 1966; 198: 1121–2,\textsuperscript{84} Scand J Urol Nephrol 1971; 5: 27–32,\textsuperscript{83} and BJU Int 2000; 86: 490–3\textsuperscript{86}</td>
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Evidence that paternity is affected by varicocele ligation in adolescence is limited. It has been shown that operated patients are fertile but there were no controls in the series and so the fate of unoperated patients is not known. It is striking that even studies with long-term follow-up make little or no mention of paternity.

Current recommendations for adolescent varicocele repair are based on the findings of persistently impaired testicular growth. The main indication for surgery is testicular hypotrophy (<2 cm or <20%) on the affected side. As growth may vary between the tests, the difference in size should be confirmed by two measurements 12 months apart. Relative indications for varicocele repair are a soft testis, bilateral grade 3 varicocele with no testicular hypotrophy, presence of varicocele in a solitary testis, poor semen analysis in a Tanner V adolescent (preferably confirmed on two specimens), and the rare conditions of pain or intra-testicular varicocele.

It is interesting to note, however, that when relatively non-invasive treatment is advocated, the criteria for surgery have been lowered. In a series from Austria of 88 adolescents and children, 94% were treated by antegrade sclerotherapy for varicoceles with equal-sized testes.

The boys and their families must be aware of the uncertainties about the significance of varicocele and the indications for surgery.

REFERENCES

37. Aho MO, Tammele OKT, Somppi EMJ, Tammele TLJ. A long term comparative follow up study of voiding, sexuality and satisfaction

380 Textbook of Erectile Dysfunction
Veno-occlusive impotence and erectile dysfunction: treatment and outcomes

Aksam A Yassin and Farid Saad

Introduction

The physiological process of erection may be viewed as interplay between three integral and inter-related processes:1

- sinusoidal relaxation;
- arterial dilatation; and
- venous compression.

In approximately 20–30% of patients with erectile dysfunction (ED) failure is due to dysfunction of the veno-occlusive system.2 Several pathological conditions can contribute to veno-occlusive dysfunction (VOD), including:

- congenital ectopic veins;
- congenital or acquired insufficiency of cavernosal tissues or the tunica albuginea (or both);
- post-traumatic or iatrogenic fistulae;
- shunts to spongiosal body or the glans penis;
- lack of neurotransmitters; and
- metabolic abnormalities, which can lead to alteration in penile microanatomy with consequences to biology and function.

Flaccidity of the trabecular smooth muscle of the corpus cavernosum of the penis plays an important role in erectile function. Under conditions of excessive adrenergic tone or impaired neurovascular status, following sexual stimulation phosphodiesterase (PDE) type 5 inhibitors act to enhance nitric oxide (NO)-mediated smooth muscle relaxation, resulting in improved penile erection in men with ED.3 Better management of ED and treatment outcomes in VOD depends on greater understanding of the physiology and pathophysiology of the penis. Such deeper knowledge of the physiology and pathophysiology depends on the knowledge of the microanatomy or the normal and pathological histology. Alteration in tissue structure can lead in turn to changes in biology and subsequently in function. After years of experience with penile venous surgery, and its disappointing short- and long-term results, we started to understand the mechanisms of VOD not only as a ‘pipeline’ concept, such as in venous anomalies, or venous valve insufficiency, either congenital or acquired, but also as a consequence of different factors leading together to veno-occlusion. It is the interplay of several microanatomical and biological substrates for penile erection. Metabolic factors are substantial in this concern.4

Step 1 in the diagnostic procedure of ED patients is the history, laboratory findings, physical examination, and basic ultrasound. For the management of VOD it is necessary to investigate (step 2) using non-invasive or less invasive procedures to evaluate the cavernosal competence or properties [intracavernosal injection (ICI), Doppler or color duplex ultrasound, and corpus cavernosum electromyography (CC-EMG)]. In step 3, it is important to evaluate penile structure and cavernosal venous circulation [cavernosography and cavernosometry, also magnetic resonance imaging (MRI)]. The data from these three steps should provide adequate information to determine the proper treatment.

Clinical management of patients with veno-occlusive dysfunction

The introduction of modern diagnostic methods and equipment, as well as better understanding of metabolic disorders affecting the penis, such as the impact of testosterone deficiency5 on erectile tissue function, has drastically enhanced our understanding of the pathology of VOD, increased the efficiency of the diagnosis of venous leakage, and facilitated the choice of the right surgical or conservative options for treatment.6

Surgical procedures

Venous ligation

Venous ligation has been known for more than 12 decades. Raymond et al., in 1895, developed a procedure to ligate penile veins for management of VOD in ED patients. This was followed by a large number of surgical procedures.6 More recently, the use of duplex ultrasound with intracavernosal injection has provided a better indication of venous leak, but cavernosometry and cavernosography are most relevant diagnostic procedures for evaluating the venous leak pattern. This can also lead to better patient selection for this surgery.

Wespes et al. investigated penile ligature–resection of the deep dorsal vein and concluded that resection of the deep
dorsal vein can restore penile erection in about 50% of well-selected patients with cavernous venous leakage. Good prognostic factors are in relatively young patients: primary erectile dysfunction with intact arterial flow, normal hormone levels, normal CC-EMG and flow-to-maintain <50 ml/minute. The failure rate is 30–50%. Success is taken to include those patients who can then obtain an erection with pharmacological agents who were unable to do so prior to surgery.6–10

Despite the mediocre long-term results of the surgical procedure and lack of preoperative predictive factors, it is difficult to believe that venous leak surgery could be offered to well-selected patients in whom the only other available alternative would be a prosthetic device.

Cakan et al. concluded that long-term success for unselected patients undergoing deep penile venous ligation is disappointing: however, careful patient selection significantly improves long-term results.11 The standard surgical procedure has a low morbidity rate. An incision of 3.8cm on the proximal dorsal site of the penis is normally sufficient. Superficial veins are first double-ligated and resected. After Buck’s fascia has been opened, sparing the neurovascular bundle, the dorsal profound veins with the circumflex veins must be resected and ligated. Generic complications include hematoma formation, infection, and necrosis. Possible specific complications include penile edema, deviation, and shortening. Extension of surgery to include the crural veins, spongiosplasty, and closure of spongio-cavernosal shunts, showed no additional advantages but higher morbidities.12

Penile revascularization or arterialization
Arterialization with the deep dorsal veins, presented by Virag et al. in 1981, showed an improvement in both arterial perfusion and the therapeutic basis of VOD.13 Anafarta et al. believed that anastomosis of the inferior epigastric artery to the deep dorsal penile vein and ligation of the vein proximally in cases of venous leakage resulted in a low success rate, probably owing to a pcancrealosal alteration in corporal tissue compliance.14 Current therapy, while effective in circumventing vascu- logenic ED, is relatively ineffective in permanently reversing the condition.15 An exact preoperative diagnosis is most essential. In patients with arteriogenic impotence, identification of concomitant corporal veno-occlusive dysfunction diagnosed by preoperative dynamic infusion cavernosography and cavernosometry may be helpful, not only in planning a more physiological surgical procedure but also in predicting long-term results. Overall, fewer than 50% of patients had good postoperative results with median follow-up of 24 months (range 19–56 months).16 Hauri’s method of arterial–venous shunt between inferior epigastric artery and the penile profound dorsal veins was published in 1984. He reported positive results, especially in patients younger than 55 years with two or fewer comorbidities.17

Venous embolization
Parona, in Italy, was the first person documented, in 1873, as performing a sclerosis of the penile dorsal vein.6 More recently, a German group presented a subset of four patients with VOD, treated by means of retrograde embolization of the internal pudendal vein. Embolization in angiographically identified pathological venous leakage might have represented a promising alternative to surgical isolation and antegrade embolization of the deep dorsal penile veins.18 However, this method has not gained recognition as a routine therapeutic approach, owing to the limited number of patients and the absence of long-term follow-up data. There is also another important consideration, in that changes in metabolic factors could affect the microanatomy of penile structures, causing alteration of erectile substrates.

Penile prosthesis implantation
The introduction of ICI therapy in the early 1980s, and later the oral PDE-5 inhibitors, led to more limited indications for penile implant surgery. This type of surgery is indicated when there is a lack of success with conservative therapies (including PDE-5 inhibitors, ICI, and vacuum device) or when the patient refuses other surgical procedures. An absolute indication for implant surgery is the severest ED with progressive venous leakage, Peyronie’s disease, or spongio-cavernosal reflux. Patient consent must be given in the knowledge of detailed information about the irreversible nature of the procedure and its potential complications, such as infection, hematoma formation, edema, rejection, pain, iatrogenic injuries, scars and deviation, as well as the potential need for re-operation.12

Conservative approaches
Long-term treatment with phosphodiesterase type 5 inhibitors
The effects of PDE-5 inhibitors are very well established in numerous animal models and clinical studies. In addition to enhancing the smooth muscle relaxation, PDE-5 inhibitors appear to play a role in ameliorating age-related changes in erectile tissues, such as fibrosis.

Ferrini et al. reported in an animal model that long-term treatment with vardenafil prevented corporal veno-occlusive dysfunction (CVOD) after radical prostatectomy by preserving smooth muscle content and inhibiting corporal fibrosis, possibly by its effect on inducible NO synthase (iNOS).19 Normalization of the dynamic infusion cavernosometry, as assessed by the drop rate and smooth muscle–collagen ratio was noted. The authors stated that long-term continuous treatment with sildenafil ameliorates age-related erectile dysfunction and the underlying corporal fibrosis in the rat.20 These data demonstrate that long-term PDE-5 inhibitor treatment corrected CVOD in the aged rat and partially reversed the age-related fibrosis and loss of smooth muscle cells (SMCs) in the corpora cavernosa, without affecting levels of oxidative stress markers, transforming growth factor-beta-1 or the Rho kinase inhibitor protein tyrosine phosphatase, nonreceptor type 11 (PTPN-11). They speculate that similar effects may be achieved with this regimen in men.20 The effects of PDE-5 inhibitors on endothelial progenitor cells can explain the endothelial recovery seen with long-term treatment. Vardenafil had been found to increase circulating progenitor cells in humans.21
Intracavernosal injection therapy

In the past 25 years, ICI therapy has led to better understanding of the pathophysiology of ED. Use of color duplex Doppler as a clinical screening method (to eliminate concomitant arterial disease) is the primary diagnostic tool. In step 3 (see above), cavernosometry, pharmaco cavernosometry, and pharmaco cavernosography can add very valuable information on intracavernosal pressure and pattern of venous leak. In 21% of patients with VOD, erectile function can be improved with pharmacological injection therapy to enable a sufficient erection for intercourse. In non-responders to monotherapy with papaverine or prostaglandin E1, a mixture of vasoactive agents as Trimix or in combination with forskolin can improve responsiveness.

Other authors have presented excellent results of four-drug intracavernous therapy for ED caused by CVOD, diagnosed by dynamic infusion cavernosometry-cavernosography (flow-to-maintain erection >10ml). Patients who were not considered suitable candidates for surgery underwent self-injection therapy. A vasoactive mixture composed of papaverine hydrochloride 12.1mg/ml, prostaglandin E1, 10.1 micrograms/ml, phenolamine mesylate 1.01mg/ml, and atropine sulfate 0.15mg/ml was used. After dose titration of the drug mixture, 54 patients (95%) were able to obtain sustained rigid erections that guaranteed satisfactory sexual activity and 69% were satisfied using the mixture. The association of the drugs used with different mechanisms of action caused a synergism that potentiated the therapeutic activity and reduced side-effects by decreasing the total drug dose.

Androgen treatment

Erectile function is a complex neurovascular process that requires input from central and peripheral nervous systems, as well as the endocrine system. The erectile response is dependent on the structural integrity of the penile tissue vascular bed and on the fibroelastic properties of cavernosal tissue. Androgens are critical for maintaining the physiological function of erectile tissue. In preclinical studies Shabsigh et al. reported that castration causes apoptosis, adversely affecting smooth muscle content and penile hemodynamics and leading to VOD. Testosterone therapy reverses these structural, biochemical, and physiological changes (Figure 50.1).

Traish et al. have demonstrated that androgens are critical for maintaining the corpus cavernosum smooth muscle responsivity, the fibroelastic properties of the corpus cavernosum, and the endothelial cell function, especially with reference to NO synthesis. Thus, androgens have a role in maintaining the integrity of penile tissues and structures, improving the response of the cavernosal nerve, smooth muscles and fibroelastic elements (Figure 50.2). Androgen deprivation in animal models, either following surgical or medical intervention, produced significant changes in the tunica, as demonstrated by electron microscopy techniques. Androgens modulate PDE-5 expression and activity. The current model of androgen action on the erectile structures proposes that penile tissue remodeling provides the link to veno-occlusive manifestations. Rogers et al. demonstrated that androgen deprivation results in VOD. Furthermore, Traish et al. noted that androgen deprivation in the animal model results in the accumulation of adipocytes in the penile subcutaneous area of the corpus cavernosum. This pathology was suggested as a potential mechanism for VOD in androgen deficiency. (Figure 50.3). The infiltration of the trabecular tissues by adipocytes in diabetic and testosterone deficient dogs (Figure 50.4) and in rats suggest that this pathological process may contribute to VOD. In humans, testosterone therapy improves erectile function in men with hypogonadism.

A number of clinical observations supporting a role for testosterone in erectile function and in the treatment of ED have been reported. There is considerable emerging clinical evidence for the management of ED with only testosterone therapy in hypogonadal patients.

A link between testosterone and ED was inferred from observations of hypogonadal patients with ED who did not respond to PDE-5 inhibitor therapy but improved with testosterone treatment. The number of circulating endothelial progenitor cells is reduced in hypogonadal men and is increased by testosterone treatment. Recently, Yassin et al. presented a case report on a dramatic improvement in penile venous leakage with testosterone administration. A detailed report was published on a series of case reports of 12 hypogonadal men with low plasma testosterone (total plasma testosterone <8nmol/l) and severe ED with varying comorbidities, such as diabetes mellitus type 1 or 2, metabolic

Figure 50.1 (a) Apoptosis in the penis of a castrated rat. (b) Replenishment with testosterone after castration causes new DNA synthesis. From World J Urol 1997; 15: 21–6.
syndrome with possible related hypertension, dyslipidemia, and obesity (Table 50.1). These patients did not respond to oral PDE-5 inhibitor therapy or maximal dosage of ICI with alprostadil. All patients underwent the standard administration of 1000mg single-dose long-acting injectable testosterone undecanoate at the start, repeated at 6 weeks and then every 12 weeks over a study period of longer than 6 months; subsequently, long-term follow-up procedures were carried out. All patients underwent dynamic infusion pharmacocavernosography at baseline, after 3 months, and after reporting improvement in erectile function following the treatment with testosterone. No residual venous leakage could be detected as early as 3–5 months in 5 patients (Figures 50.5, 50.6, 50.7, 50.8).

These 5 patients reported significant improvement in erectile function compared with baseline within 12–21 weeks.
of androgen treatment, as evidenced by clinically relevant increase in their erectile function (EF) domain (questions 1–5 plus question 15) of the International Index of Erectile Function (IIEF) when compared with baseline values (Table 50.2). Pharmacocavernosography and repeat radiological studies in patients who reported improvement in erectile function did not show veins draining the corporal bodies (see Figures 50.5, 50.6, 50.7, 50.8). All patients noted improvement in the sexual desire domain. Notably, a sixth patient exhibited improved erectile function and absence of venous leakage after 11.5 months of treatment (see Figure 50.6); therefore, this patient was considered to be a late responder to the study therapy (see Table 50.2). The remaining 7 patients with persistent venous leakage are still under follow-up observation. Currently, these patients are entering the 24th month of the therapy. Plasma testosterone levels and other biochemical markers were monitored in long-term follow-up for efficacy and safety evaluation of the therapy. The results are summarized in Table 50.3.

In a recent report by Kurbatov et al. 19 hypogonadal men (testosterone level <12nmol/l), aged 32–56 (44±8.3) years, non-responders to PDE-5 inhibitors and with venous leakage from corpora cavernosa (demonstrated by sophisticated and impressive MRI methods) were treated with testosterone.40 A total of 13 of the 19 patients (68.4%) had restored sexual activity (Figure 50.9).

We can suggest or hypothesize that penile venous leakage could be a metabolic disorder that can be reversible in some cases with testosterone replacement, rather than a purely physical lesion. This hypothesis should be tested in further studies. We propose that the standard monotherapy with testosterone produces structural remodeling processes of the penile tissues, ultimately leading to venous leakage correction and significant improvement of symptomatic ED.

Vacuum devices
Vacuum devices are a non-invasive, successful, and cheap therapy and they have good acceptance. In 1974, Osbon

Table 50.1 Patients’ characteristics

<table>
<thead>
<tr>
<th>Patients’ characteristics, demography and comorbidities</th>
<th>All subjects (n=13)</th>
<th>Non-responders (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>58</td>
<td>66</td>
</tr>
<tr>
<td>Age range</td>
<td>39–73</td>
<td>52–73</td>
</tr>
<tr>
<td>Mean age ± SD (years)</td>
<td>58.3 ± 9.7</td>
<td>59.9 ± 9.1</td>
</tr>
<tr>
<td>ED severity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild and moderate</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Severe</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>Mean IIEF erectile function domain</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>ED etiology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organic</td>
<td>13 (100%)</td>
<td>6</td>
</tr>
<tr>
<td>Psychogenic</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mixed</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total serum testosterone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2.0ng/ml</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>2.1–3.4ng/ml</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Mean IPSS</td>
<td>15</td>
<td>19</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Type I diabetes</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Type II diabetes</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>BPH/LUTS</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Non-defined etiology</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

SD, standard deviation; ED, erectile dysfunction; IIEF, International Index of Erectile Function; IPSS, International Prostate Symptom Score; BPH, benign prostatic hyperplasia; LUTS, lower urinary tract symptoms. From reference 41.

Figure 50.5 X-ray of a 56-year-old patient with type 2 diabetes, metabolic syndrome and erectile dysfunction at baseline; initial testosterone level 1.8ng/ml, and non-responder to phosphodiesterase type 5 inhibitors or alprostadil 20µg. (b) Cavernosography 12 weeks after initiation of testosterone treatment. There are no signs of venous leakage. From Andrologia 2006; 38: 34–7.
Veno-occlusive impotence and erectile dysfunction: treatment and outcomes

**Figure 50.6** (a) A 63-year-old patient with type 1 diabetes, metabolic syndrome, and severe hypogonadism at baseline; initial testosterone level 1.07 ng/ml, and non-responder to phosphodiesterase type 5 inhibitors or alprostadil 20 µg. Abnormal cavernosography showing venous leakage in the superficial and deep veins. (b) Absence of venous leakage evident by cavernosography after 4.5 months on testosterone undecanoate, with better ‘penile composition’ and corporal opacification. From J Sex Med 2006; 3: 727–35.41

**Figure 50.7** (a) Cavernosography of a 61-year-old patient with metabolic syndrome and type II DM; initial testosterone level 2.1 ng/ml, and non-responder to phosphodiesterase type 5 inhibitors or alprostadil 20 µg. (b) Control dynamic infusion pharmacocavernosography (DIPC) after 21 weeks of therapy with injectable testosterone undecanoate: testosterone level 5.1 ng/ml, with better penile corporal opacification. After combination with 50 mg sildenafil the VOD of superficial veins had no negative effect on erectile quality. From J Sex Med 2006; 3: 727–35.41

Delivered the commercial system to the US market. The principle is to force blood flow into the penis by means of vacuum induction by inserting the penis in a vacuum cylinder. With a restriction rubber ring placed at the base of the penis, venous outflow can be prevented so erection can take place and be maintained. This method has a high success rate and it is well accepted in older patients with a personal preference for this device or with severe comorbidities. The ring must be removed after intercourse, and should not be in place for longer than half an hour. Advantages are its possible application in ED due to all etiologies, its ease of use, and its very low side-effect profile. Potential disadvantages are retrograde or decreased ejaculation as a result of the restriction ring, skin bleeding, coldness and extreme penile congestion, and occasionally decreased erection during sexual intercourse.
there may be an endocrine mechanism behind the disorder. Estradiol plasma concentrations were significantly higher in venous leakage patients compared with controls, suggesting that the steroid environment, in particular the estradiol level, can influence venous vascular tone (via vascular endothelial growth factor or NO), thus affecting venous leakage. Recently, it has been shown that there are a reduced number of circulating endothelial progenitor cells in hypogonadal men, suggesting that hypotestosteronemia may be associated

### Table 50.2 International Index of Erectile Function scores of erectile function (EF) and sexual desire (SD) in early and late responders (six patients) compared with non-responders at baseline and at 12, 30, and 46 weeks follow-up

<table>
<thead>
<tr>
<th>Responders (n=6)</th>
<th>Baseline</th>
<th>Week 12</th>
<th>Week 30</th>
<th>Week 46</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early responders:</strong> (N=5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EF</td>
<td>8.0 (±0.00)</td>
<td>23.4 (±0.80)</td>
<td>24.4 (±0.40)</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>4.0 (±0.00)</td>
<td>8.0 (±0.00)</td>
<td>8.0 (±0.00)</td>
<td></td>
</tr>
<tr>
<td><strong>Late responders:</strong> (N=1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EF</td>
<td>7.0 (±0.00)</td>
<td>4.0 (±0.00)</td>
<td>17.0 (±0.00)</td>
<td>24.0 (±0.00)</td>
</tr>
<tr>
<td>SD</td>
<td>4.0 (±0.00)</td>
<td>7.0 (±0.00)</td>
<td>7.0 (±0.00)</td>
<td>7.0 (±0.00)</td>
</tr>
<tr>
<td><strong>Non-responders (n=6)</strong></td>
<td></td>
<td></td>
<td></td>
<td>Follow-up in progress</td>
</tr>
<tr>
<td>EF</td>
<td>6.71 (±1.21)</td>
<td>10.28 (±2.11)</td>
<td>11.28 (±2.70)</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>4.0 (±0.00)</td>
<td>7.42 (±0.52)</td>
<td>7.85 (±0.15)</td>
<td></td>
</tr>
</tbody>
</table>

From reference 41.

### Future directions

Tan et al. proposed that ED is the most common symptom in hypogonadal subjects.51 The percentage of patients with testosterone deficiency and ED ranges between 12% and 36%. We found, from screening an ED population, that 18.3% are identified as hypogonadal.52 Guay et al. reported that 37% of their ED patients had had hypogonadism.53 In functional insufficiency of veno-occlusion, it has been hypothesized that...
Table 50.3 Follow-up protocol and measurements at baseline and regular check-ups at 3, 6, and 12 months afterwards

<table>
<thead>
<tr>
<th>Late responder (n=1) follow-up protocol</th>
<th>Baseline</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal girth (cm)</td>
<td>121</td>
<td>116</td>
<td>115</td>
<td>107</td>
</tr>
<tr>
<td>Prostate sonogram ± TRUS (ml)</td>
<td>48/15</td>
<td>48/16</td>
<td>46/16</td>
<td></td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td>130/80</td>
<td>125/75</td>
<td>130/80</td>
<td>125/86</td>
</tr>
<tr>
<td>IIEF EF</td>
<td>7.0</td>
<td>4.0</td>
<td>17.0</td>
<td>24.0</td>
</tr>
<tr>
<td>SD</td>
<td>4.0</td>
<td>7.0</td>
<td>7.0</td>
<td>7.0</td>
</tr>
<tr>
<td>AMS</td>
<td>55</td>
<td>49</td>
<td>38</td>
<td>36</td>
</tr>
<tr>
<td>IPSS</td>
<td>16</td>
<td>14</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>PSA (free)</td>
<td>0.81</td>
<td>1.15</td>
<td>1.16</td>
<td></td>
</tr>
<tr>
<td>Testosterone</td>
<td>1.81</td>
<td>4.54</td>
<td>4.9</td>
<td>5.2</td>
</tr>
<tr>
<td>SHBG</td>
<td>196</td>
<td>88</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>DHEA-sulfate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leucocytes</td>
<td>8.6</td>
<td>6.0</td>
<td>6.0</td>
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</tr>
<tr>
<td>Erythrocytes</td>
<td>4.2</td>
<td>5.85</td>
<td>5.04</td>
<td></td>
</tr>
<tr>
<td>Thrombocytes</td>
<td>115</td>
<td>197</td>
<td>152</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>12.8</td>
<td>14.7</td>
<td>14.0</td>
<td></td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>40</td>
<td>46</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>Glycosylated hemoglobin</td>
<td>7.8</td>
<td>6.7</td>
<td>6.8</td>
<td>6.6</td>
</tr>
<tr>
<td>Blood glucose</td>
<td>145</td>
<td>130</td>
<td>120</td>
<td>116</td>
</tr>
<tr>
<td>Lipids</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>316</td>
<td>257</td>
<td>161</td>
<td>188</td>
</tr>
<tr>
<td>HDL</td>
<td>38</td>
<td>na</td>
<td>na</td>
<td>47</td>
</tr>
<tr>
<td>LDL</td>
<td>70</td>
<td>na</td>
<td>55</td>
<td>55</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>468</td>
<td>368</td>
<td>244</td>
<td>220</td>
</tr>
</tbody>
</table>

TRUS, transrectal ultrasound; IIEF, International Index of Erectile Function; AMS, Aging Male Symptoms Score; IPSS, International Prostate Symptom Score; PSA, prostate-specific antigen; SHBG, sex hormone-binding globulin; DHT, dihydrotestosterone; HDL, high-density lipoprotein; LDL, low-density lipoprotein. From reference 41.

Figure 50.9 MRI of venous leak in a hypogonadal man (a) before and (b) after 21 weeks of treatment with injectable long-acting testosterone undecanoate.
with low numbers of these cells.\textsuperscript{55} The fact that testosterone therapy results in an increase in these cells, through a possible direct effect on the bone marrow, suggests a profound role for androgens in erectile function.\textsuperscript{39} Newer diagnostic methods, such as duplex ultrasound or MRI of the penis, which can detect and visualize venous leakage in patients, may be useful in evaluating the effect of novel therapeutic approaches to treat VOD (e.g. androgens, PDE-5 inhibitors, or a combination of both).\textsuperscript{46} We will have to await further preclinical research outcomes to judge whether other novel approaches, such as gene therapy, will be effective in managing this specific pathology of ED.

REFERENCES

27. Traish AM, Goldstein I, Kim NN. Testosterone and erectile function: from basic research to a new clinical paradigm for managing men with androgen insufficiency and erectile dysfunction. Eur Urol 2007; 52: 54–70.
Penile fracture: evaluation and management

Osama KZ Shaeer and Kamal ZM Shaeer

Introduction

‘Fracture of the penis’ is the term describing traumatic rupture of the tunica albuginea of the corpus cavernosum, secondary to blunt trauma inflicted when the penis is in the erect state, most commonly during sexual activity. The consequent pain and swelling is usually the cause of presentation; however, despite a consistent and classical clinical picture, many controversies surround the guidelines for optimal management.

Penile fracture is by far the most commonly reported blunt injury to the penis, although an exact incidence cannot be stated. Penile fracture was reported in 183 publications between 1996 and 2001, discussing a total of 1331 cases. Variation in prevalence according to geographic distribution is evident, mostly on account of diversity of sexual cultures and practices. The vast majority of the 1331 cases reported came from the Middle East; namely Iran, Morocco, Turkey, Egypt, and Saudia Arabia. The USA and Canada came second in rank. Patients were mostly in the fourth decade, with the age range between 12 and 82 years.

Pathogenesis

Erection is a prerequisite to rupture of the tunica albuginea in response to blunt trauma or bending, since the high intracorporal pressure in the erect state stretches the tunica to its limit, thinning it out and rendering it fragile. Forceful bending at this state will lead to a surge of intracorporal pressure that stretches the already taut tunica beyond its limit, causing it to rupture. Bending an erect penis can cause pressure to increase from 180 mmHg to 1500 mmHg. In contrast, a flaccid penis will bend and yield in response to blunt trauma with relatively no rise in intracorporal pressure.

Rupture of the tunica albuginea is usually painful as well as audible (a snapping sound). Blood contained in the corpus cavernosum gushes out, resulting in immediate detumescence, and formation of a hematoma. Edema of penile skin follows.

The tear in the tunica albuginea is mostly unilateral though bilateral tears have been reported. The tear is usually transverse or oblique; nevertheless, longitudinal tears are also encountered. Rupture usually occurs in the proximal shaft but has also been described in the distal third of the penis and, rarely, in the crus.

Rupture of the tunica mostly occurs on the ventral aspect of the penis, particularly if a coital injury is the cause. This can be explained both by the mechanism of injury (direction of the arm of force) and by the sturdy nature of the dorsal aspect of the penis in comparison with the ventral aspect. The tunica albuginea is thicker dorsally than ventrally, and is less liable to stretch beyond its limit in the erect state, thus preventing the erect penis from bending ventrally. It is therefore less liable to rupture. The dorsal aspect is further supported by the neurovascular bundle. In case of overwhelmingly forceful ventral bending, the dorsal vessels are more liable to snap than is the dorsal tunica albuginea, and the resulting pain usually brings the traumatic force to a stop, protecting the dorsal tunica from further development of pressure. Accordingly, ventral bending of the erect penis is less likely than dorsal bending, and thus ventral rupture is more likely than dorsal rupture.

Nevertheless, though it is rare, dorsal rupture of the tunica albuginea does occur.

Injury of the urethra is widely reported as a complication of penile fracture, occurring in up to 38% in one case series, and ranging from partial injury to complete disruption. A clear variation in the incidence of urethral injuries has been noticed in correlation with the modality of trauma, being higher in coital injuries. This was explained by the higher magnitude of force with coital trauma in comparison with manipulation injuries.

If surgical repair is not undertaken, the defect usually heals by secondary intention, and the hematoma becomes organized and encapsulated. The healed tear in the tunica albuginea is relatively weak and is therefore liable to aneurysmal dilatation and may be the site of venous leakage, resulting in erectile dysfunction (ED). The neglected hematoma may lead to abscess formation or deformity.

Although fracture of the penis implies rupture of the corpus cavernosum, the resultant hematoma may be exacerbated further by associated injuries, such as rupture of the superficial vessels of the penis or tears in Dartos muscle or in Buck’s fascia, which is firmly adherent to the tunica albuginea.

Etiology

Traumatic event

Penile fracture is the result of blunt trauma or bending force applied to the erect penis. The causative incident is almost
always related to sexual activity, whether coital or non-coitale. In coital mishaps, the erect penis accidentally propels into the partner’s perineum or pubis. This event can occur in any sexual position, but is more likely to occur in the female dominant position, the so-called reverse coitus. Variation in the traumatic event is noticeable in different geographic regions. The previously mentioned coital injuries are the main cause of fracture penis in the USA and Europe. In contrast, in the Middle East, non-coital injuries (primarily during masturbation) are relatively more common. This can be attributed to religious and social prohibition on pre-marital and extra-marital sex, with possible consequent inclination to masturbation until marriage.

In addition to aggressive masturbation, non-coital fractures are caused by intentional bending of the erect penis to induce detumescence. The latter is a cultural habit reported in some Middle Eastern countries, where it is referred to as taqaanadan or golje shkestan (meaning ‘to click’ or ‘to snap’). The erect penis is pushed forcibly downwards, upwards, or laterally to achieve detumescence or pleasure, in many cases habitually.

Other rare incidents and modalities of trauma have been reported, including attempts at manual correction of a congenital chordee, attempts to tuck an erect penis into underwear, falling from the bed onto an erect penis during sleep, rolling over in bed during nocturnal tumescence, and masturbating with the tubing of a vacuum cleaner.

Predisposing factors
To date, factors predisposing to penile fracture have been ambiguous. An association was noted with Peyronie’s plaques in four penile fracture cases. This was theoretically explained by aberrant elasticity and deviation of the penis in the erect state, both rendering the penis more prone to trauma upon sexual activity. In addition to Peyronie’s disease, fibrosclerosis of the tunica albuginea and chronic cell infiltrates were observed in five cases of fracture penis. Periurethral inflammation, as occurs in gonococcal urethritis, was also noted in association with penile fracture.

Clinical picture
The unique and classical clinical picture notorious to fracture of the penis may suffice in many instances for a clinically based diagnosis without resorting to investigations. Presentation may be early or late, depending on the extent of injury that is the motivation to seek urgent medical assistance if significant, availability of specialized medical expertise, as well as other social circumstances.

Early presentation
Blunt trauma to the erect penis sufficient to cause rupture of the tunica albuginea results in a tell-tale cascade of events: acute pain mostly during sexual intercourse, a characteristic popping or snapping sound, immediate detumescence, progressive swelling, and ecchymosis.

Initially, the ecchymotic swelling increases progressively, as does edema of the penile skin. After a brief period, progression of the hematoma declines, probably owing to detumescence and pain-induced vasoconstriction, both of which arrest the bleeding. Distribution of the hematoma depends in part on the integrity of fascial layers of the penis. If Buck’s fascia is intact, ecchymosis is confined within Buck’s fascia over the tear, and the patient has a well-defined collection and the so-called eggplant deformity. When Buck’s fascia is compromised, the collection seeps to Colles’ fascia, in which case extravasation is diffuse and assumes a ‘butterfly’ pattern over the perineum, scrotum, and lower anterior abdominal wall.

In cases of early presentation, this distribution may be masked by edema. It should be noted that the hematoma does not necessarily coincide with the defect. If Buck’s fascia is torn, blood may proceed to Colles’ fascia and assume a wide, non-specific distribution. Patients may have angulation of the penis, commonly away from the site of rupture. Deviation in this early stage is caused by hematoma and edema.

The defect may be palpable over the fracture site, referred to as the ‘rolling sign’. The tenderness encountered and the overlying swelling and edema may prevent palpation of the defect without causing significant discomfort to the patient. This sign is best elicited under anesthesia. Injury of the urethra is not uncommon, and usually manifests itself by bleeding from the urethral meatus or frank hematuria. Retention of urine and a weak stream are possible presentations. Bleeding from the urethra does not necessarily imply rupture of the urethra. In some cases with mental bleeding, ascending urethrography excludes urethral rupture, while urethroscopy demonstrates mucosal injury rather than frank rupture.

Late presentation and complications
If a fractured penis is neglected, the initial manifestations, namely edema and hematoma, subside gradually. Patients with delayed presentation usually report the classic history but also complain of the resulting complications, such as ED, penile deviation, and a palpable mass, erectile dysfunction, or penile deviation. ED is caused by possible venous leakage at the site of the healed tear. Deviation may be caused by contracture of scar in the tunica albuginea or by organization of the hematoma. Contrary to the initial early deviation that follows fracture, late deviation may be towards the ipsilateral side of the healing tear and hematoma, the opposite side of the initial earlier deviation. Less frequently, patients may present with poor urinary stream, urinary retention, a urethro-cavernous, or a urethrocutaneous fistula.

Atypical presentation
In rare incidents, the characteristic story of penile fracture is not evident. The relationship of the onset to sexual activity may not be reported, commonly on account of embarrassment, and less frequently because of a failure to correlate the sexual act with the symptoms on the part of the patient. Fractures close to the pubic insertion of the corpora may result in scrotal and perineal pain, and a totally normal penis, and may be misdiagnosed and managed as epididymo-orchitis. The correct diagnosis may be reached by cavernosography.
Recurrent fracture
Penile refracture following surgical repair of an initial instance has been described in a few case reports.\textsuperscript{27-29} In one case, refracture occurred 10 weeks after repair of the initial fracture, and was associated with extension into the urethra, unlike the initial fracture, in which there was no urethral injury. Refracture was attributed to early resumption of sexual activity, specifically vigorous intercourse. This emphasizes the importance of abstinence following repair. Non-absorbable sutures have been suggested as a measure taken to avoid refracture.\textsuperscript{29}

Differential diagnosis
Several conditions may simulate fracture of the penis. Rupture of the deep dorsal vein is one of the most common. In one study, 2 out of 21 cases with the classic picture of fracture penis had intact corporeal bodies and a ruptured deep dorsal vein.\textsuperscript{30} Less commonly reported are rupture of the dorsal penile artery and non-specific internal hemorrhage.\textsuperscript{12}

A rare entity is ruptured Mondor’s disease of the penis. Mondor’s disease is thrombosis of the superficial dorsal vein of the penis, usually related to trauma, including sexual intercourse. Thrombophlebitis may occur on top, rendering the dura vulnerable and prone to rupture upon coital trauma. Ruptured Mondor’s disease therefore exhibits a similar sequence of events to those of a fractured penis: acute pain and a popping sound during coitus. A recent history of a painful, firm, cord-like structure on the dorsum of the penis, possibly extending to the inguinal region, may be suggestive.\textsuperscript{31}

Considering that rupture of the corpus cavernosum occurs mostly ventrally, a hematoma oriented on the dorsal aspect of the penis should raise questions as to other possibilities. Imaging, especially cavernosography, may discriminate between the aforementioned possibilities. In many situations, surgical exploration alone can reveal the underlying pathology.

Investigations
Diagnosis of penile fracture may be established solely on clinical grounds considering the characteristic sequence of events and the possibility of directly palpating the defect in the tunica albuginea. Exclusive dependence on clinical impression is advocated by some authors, based on the experience that radiological assessment contributes little to decision-making,\textsuperscript{32} especially with surgical exploration being inevitable in the opinion of the majority. In addition, investigations are subject to availability of expertise and equipment, which may be an obstacle. Considering the invasive nature of some of the diagnostic tools, patient disapproval may be encountered.\textsuperscript{33}

On the other hand, investigations can help to ascertain the diagnosis, localize the site and number of breaches in the tunica, identify the presence of associated complications, and exclude other possible diagnoses. This in turn may influence the treatment plan and whether a conservative or surgical approach is undertaken.

Ultrasonography
The defect in the tunica albuginea may be palpated directly or its site deduced from the overlying hematoma. Amidst tense edema and tenderness, it can be difficult to determine the site of the hematoma and more importantly the site of the defect in the corporeal bodies by palpation. Both the hematoma and defect can be delineated by ultrasonography\textsuperscript{34} without causing patient discomfort. Ultrasonography is fast, reliable, and non-invasive. However, a contradictory opinion is that ultrasonography may fail to localize the exact site of the tear (as checked by surgical exploration) and may fail to diagnose multiple tears.\textsuperscript{32} Instead, it gives provisional information about the probable site of the tear, by demonstrating the hematoma.

Cavernosography
Cavernosography is capable of accurately demonstrating the site and number of defects in the tunica albuginea. It can also diagnose some of the possible complications such as a caverno-urethral fistula.\textsuperscript{6} Despite its value and accuracy, some authors believe that cavernosography will unnecessarily delay surgery.\textsuperscript{31} The same information issued by cavernosography can be obtained upon surgical exploration, which is in many cases inevitable. Furthermore, cavernosography has been reported to yield false negative results in some cases, as checked by surgical exploration, where a tunical breach found upon exploration is not demonstrated in the cavernogram.\textsuperscript{6} Cavernosography cannot exclude vascular injuries that may be the underlying pathology, rather than disruption of the tunica albuginea, thus giving a misleading indication for conservative management.\textsuperscript{30}

The painful and invasive nature of this examination and the possible complications (including infection and allergy to the dye used) may discourage its application. It is my opinion that cavernosography may be reserved for decision-making in ambiguous cases with atypical presentation, such as those with crural rupture manifesting with scrotal pain and a normal penis,\textsuperscript{7} cases of late presentation and non-progressive course where conservative management is a possible option, and cases with suspicion of a caverno-urethral fistula, in which cavernosography is the diagnostic modality of choice.\textsuperscript{35}

Urethrography
Retrograde urethrography is well indicated in cases with hematuria or difficult micturition. Nevertheless, urethrography has demonstrated urethral tears in cases of penile fracture with neither mental bleeding nor micturition problems. It is not yet agreed whether this justifies routine application of urethrography for cases with penile trauma.\textsuperscript{8}

On the other hand, urethrography may give false negative results. Bleeding from the urethra may be on account of injury of the urethral mucosa rather than because of a frank tear. Mucosal injury is diagnosed by urethroscopy rather than urethrography.\textsuperscript{17}

Urethroscopy
Exploration of the urethral mucosal surface following fracture of the penis has demonstrated injury of the mucosa despite a
negative urethroogram. Flexible cystoscopy is more suitable for this purpose but cannot be advocated for routine use.

**Magnetic resonance imaging**

Accuracy of magnetic resonance imaging (MRI) has been verified by several reports, one of which ascertained its superiority over ultrasonography and cavernosography in ambiguous cases. Despite its accuracy, MRI cannot be recommended for routine use in the diagnosis of fractured penis considering the time and cost involved. It can be a valid option in vague cases where clinical examination and the aforementioned investigations neither confirm nor exclude a defect in the tunica albuginea, and conservative treatment is strongly considered.

To sum up, imaging is a useful adjunct to clinical diagnosis, especially in cases with atypical presentation or those in which conservative treatment is an option to be considered. Nevertheless, surgical exploration is still the gold standard for the evaluation and management of suspected penile fracture, and whenever indicated, it should not be delayed awaiting the availability of a diagnostic measure.

**Treatment**

Prior to intervention, adequate patient counseling is mandatory, and so is a written informed consent. The mainstay in the management of suspected fracture of the penis is immediate surgical exploration. Nevertheless, controversy still exists. Some experts advocate delayed repair. Others recommend conservative treatment in selected cases. Each of these opinions has its rational basis.

**Choice of treatment**

Most authors advocate urgent surgical intervention for cases of suspected penile fracture. Unintentional delay of the repair up to 48 hours (depending on the time of presentation) was not associated with exceptional difficulty or exaggerated complications in comparison with immediate repair. Intentional delay for 7–12 days has been suggested, allowing resolution of edema and organization of the hematoma, in which case the hematoma would be clearly palpable and would then be taken as a guide for an incision at the site of the tear in the tunica albuginea. There are reports of successful outcome with this approach, without significant complications. Nevertheless, the site of the hematoma may be misleading, since it does not always lie over the tear. Moreover, delayed repair may lead to prolongation of morbidity and possibly a heavier psychological impact.

As to conservative treatment, its advocates base their opinion on experience with patients who were not operated upon, either because of patient disapproval of surgical intervention or because of delayed presentation. This subset of patients did exhibit a higher rate of complications in comparison with those who were operated upon, but the complications were not significant enough in frequency and magnitude to rule out conservative treatment completely. A review of the literature reported complication rates of 29% and 0% for conservative and operative approaches, respectively. Another review reported complication rates of 40.7% and 8.2%, respectively. Complications issuing from conservative treatment included pain, ED, urethral stenosis, and persistent hematoma. In favor of conservative treatment is the shorter hospital stay and lower physical burden.

No clear-cut guidelines have been proposed for patient selection to receive conservative treatment or surgery. While patient rebuttal of surgery is an absolute indication for conservative therapy, other indications include milder cases without major progressive tissue swelling, without urinary complications, without deformity, without an extracorporal source of bleeding and with intact corporeal bodies as confirmed by imaging techniques. Cases with delayed presentation and promising clinical condition may also be candidates for the conservative approach.

**Principles of surgical repair**

The procedure should be performed under antibiotic coverage. Palpation of the defect and imaging techniques such as cavernosography and urethrography may guide the surgical plan, and can be performed intra-operatively under anesthesia. A trial at urethral catheterization may commence the procedure. If this fails, options are cystoscopy and catheterization along a guidewire, or suprapubic cystostomy. Some authors recommend a cautious approach to catheterization so as to reduce the risk of infection and further trauma to the urethra.

Several incisions have been proposed for exploring the penile shaft, the most popular of which is the circumferential subcoronal degloving incision. The hematoma is evacuated and ‘bleeders’ in Buck’s or Dartos layers are ligated. The three corporeal bodies are inspected for defects. This may be assisted by injection of methylene blue or saline into the corpora and through the meatus. The irrigation fluid flows back from the defect (if present), facilitating identification. When a defect in the tunica albuginea of the corpora cavernosa is encountered, the edges are freshened and sutured ‘water-tight’ in the direction of the defect. In the case of a longitudinal defect, if narrowing is anticipated, the edges are approximated transversely. In some instances, a transverse defect in the tunica may proceed medially behind the corpus spongiosum. In such cases, subtle mobilization of the spongiosum may assist full exposure and repair. The shaft should be explored for a second defect. This, as well as competence of the repair, can be checked by repeating the previously mentioned transcorporal irrigation.

Continuous sutures are more ‘water-tight’. Relaxing interrupted sutures across the continuous suture line will support the latter and help prevent dehiscence upon future erections. Interrupted stitches are adopted by some authors, especially in cases of penile refraction. Absorbable or non-absorbable suture materials are a matter of personal preference. If non-absorbable stitches are to be used, the knots should be inverted. Non-absorbable suture materials were recommended following some instances of penile refraction. Although no clearly definitive information is available, it seems that the type of suture material used is not critical, much the same as with abdominal fascial closures. I recommend slowly absorbable suture materials such as
polydioxanone, to maintain a good balance between the virtues of the two.

As to urethral injuries, an indwelling catheter may suffice for a tiny defect to heal. Suprapubic cystostomy is also a possible resort if catheterization fails. Larger defects should be formally repaired by freshening and suturing the edges, preferably in two layers, and diverting urine for a sufficient period postoperatively. An end-to-end anastomosis may be necessary in the rare cases of complete transection of the urethra.46

The utility of a drain is controversial,3 since its value in drainage may be compromised by the possibility of introducing infection. The penis should be dressed in the vertical position to decrease edema. Dressing should be snug but never tight enough to cause skin necrosis.7 Postoperative antibiotic coverage and analgesia are prescribed. The use of antierectogenic drugs for the convalescence period is controversial.47

The catheter is usually removed on postoperative day 2 unless urethral injury is suspected. Dressing is removed on postoperative day 7.41 Abstinence from sexual activity for an adequate period of time is important to avoid penile refracture. Although the healing time of tunical tissue is not known, it seems appropriate for patients to remain sexually abstinent for a minimum of 6 weeks and to refrain from high-impact sexual activity thereafter.29

The choice of incision for the repair of penile fracture is probably a matter of custom or preference.7 A subcoronal circumferential degloving incision is one of the most popular, allowing excellent exposure of the three corpora46 but it may be complicated by lymphedema.3 It is my experience that the postoperative erections may pull on the suture line and result in gaping in some cases, especially with the sutures tearing through edematous skin. A horizontal semicircular incision on the ventral aspect of the distal penis has been proposed, preferably in the area that suffers edema the least. This incision is more secure to gaping upon erection, and the shaft can be delivered through it.21 A direct longitudinal incision over the presumed site of fracture may provide simple direct access, but may also be misleading since the hematoma does not always coincide with the defect,21 and may give poor cosmetic result.

A high scrotal midline raphe incision avoids the excessive dissection in the process of degloving and is relatively concealed with better cosmetic outcome. It can also be a route for a proximal degloving procedure. A suprapubic incision gives access to the three corporeal bodies and is away from the edematous area. However, access to the ventral aspect of the penis is more difficult in comparison with the subcoronal incision. With several options for the incision, none is unanimously adopted, or ideal for all situations.3

**Principles of conservative treatment**

Conservative treatment comprises cold compresses, pressure dressings, and anti-inflammatory drugs. Antibiotics are used empirically in some cases although no evidence exists as to their value.1 The use of sedatives and estrogens to suppress erection during convalescence is probably unnecessary.48 Furthermore, it has been suggested that the presence of erections after a penile fracture reduces the patient’s anxiety about impotence and may have an overall beneficial psychological effect.1 Although patients with urethral injuries are not recommended for conservative treatment, those who do decline surgery may receive a suprapubic cystostomy or a transurethral catheter, which should be left in place for 1–6 weeks under antibiotic prophylaxis.41

**REFERENCES**

Penile fracture: evaluation and management

Risks, complications, and outcomes of penile lengthening and augmentation procedures

Hunter Wessells and Jack W McAninch

Introduction

Elongation of the penis has been contemplated since antiquity, but only since 1971 has it been carried out as a reconstructive surgical technique for congenital and acquired shortening of the penis. Cosmetic penile enlargement began with girth enhancements in Miami in the late 1980s, but it was the Chinese surgeon Long who in 1990 described division of the suspensory ligament and penile skin advancement as a cosmetic procedure to increase penile length. Since then, over 10,000 men have undergone penile lengthening and girth enhancement, although no peer-reviewed paper has reported a reliable description of the techniques or results. The risks, both cosmetic and medical, have never been described by the proponents of the operations, and the complication rate is unknown. Interest in the procedures remains intense, despite action by the California Medical Board against one of the major proponents. A full understanding of penile enlargement is therefore necessary for urologists and plastic surgeons, who may be called upon to treat the complications of these procedures. This chapter reviews the indications, techniques, risks, complications, and results of penile lengthening and girth enhancement, and discusses considerations in the reconstruction of failures.

Indications

Penile lengthening procedures have traditionally been reserved for patients who suffer severe shortening of the penis as a result of epispadias, trauma, Peyronie’s disease, or failed penile implant. The definition of micropenis in the neonate is established as greater than 2.5 standard deviations below normal, or 2.5 cm stretched length. In adults, controversy exists as to the definition of a penis small enough for lengthening. It is unclear whether the flaccid or erect length is an appropriate guideline, or whether normal men should be considered for the procedure, since even men with the smallest most deformed penises can have appropriate sexual relationships.

However, despite such arguments, penile enlargement surgery continues unabated for esthetic reasons and to improve self-esteem. Anecdotally, most men desire increase in flaccid length and girth in response to a ‘locker room’ mentality, but erect length is mentioned as motivation by others. It is unlikely that these procedures will go away; rather, with improvements in technique, they may become routine cosmetic surgical procedures.

Technique

The detail in this section on techniques is meant to give the reader enough familiarity with the methods of penile enlargement to allow patient counseling and to guide reconstruction of failed operations. The authors’ experience with penile lengthening comes not in physically normal men, but only in those men with traumatic loss of penile length.

Penile lengthening

Early reports of penile lengthening describe division of the suspensory ligament and mobilization of the proximal crura off the inferior pubic rami. Because of the risk of injury to the neurovascular structures of the penis, cosmetic surgery for penile lengthening relies on division of the suspensory ligament and skin flap advancement to increase the pendulous penile length. The corpora cavernosa, fused along the distal three-quarters, are attached to the pubic symphysis by the suspensory ligament; this structure, a condensation of Buck’s fascia, maintains penile position during coitus.

Division of the ligament can be accomplished through a variety of infrapubic incisions, but the technique is straightforward. By dissecting just below the pubic bone, hugging the periosteum, the relatively broad, dense fibrous tissue can be released while avoiding injury to the cavernous arteries and nerves. The more superficial fundiform ligament is encountered prior to identification of the suspensory ligament, but does not contribute to the position of the penis.

Choice of incision is more important from the perspective of skin flap advancement and wound healing than exposure of the suspensory ligament. Long described an M-shaped skin incision, while Roos developed an inverted VY flap for skin advancement, which was ‘modified for the Western male’ to deal with problems of angulation (Figure 52.1). Rosenstein has the distinction of popularizing the inverted V flap in the USA and of starting the risky but profitable industry of penile...
enlargements.\textsuperscript{8,20} This incision has several drawbacks: these include poor healing at the intersection of the limbs of the inverted Y owing to excess tension; advancement of hair-bearing skin onto the shaft, resulting in ‘scrotalization’ of the penis; and dog-ears on the scrotal margins. Experience in treating complications of the VY plasty led Alter to adopt a double-Z-plasty to expose the suspensory ligament and advance skin onto the penile shaft without tension (Figure 52.2).\textsuperscript{21} He also advocates the insertion of autologous or synthetic material to fill the dead space created by release of the ligament, preventing re-attachment of the penis in its original location.

\begin{figure}[h]
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\caption{(a) Double-Z-plasty skin advancement. (a) Initial incision. (b) After skin closure.}
\end{figure}

\textbf{Girth enhancement}

Enlarging the girth of the penis may be esthetically desirable if penile length is also increased, thus maintaining the normal aspect ratio of the penis.\textsuperscript{22} Two methods have been proposed to enhance penile girth – injection of harvested autologous liposuction specimen and surgical placement of a dermal-fat composite free graft around the penis.

Injection of liposuctioned fat from the abdominal wall or inner thighs was popularized by Rosenstein, but has several potential pitfalls.\textsuperscript{20} The harvested fat is injected into the dartos fascia through several small incisions at the base or corona. Distribution of fat may be irregular, or the fat may migrate in the early postoperative period, leading to nodular deposits of fat with resultant penile deformity (see Complications, below). Human fat grafts lose weight and volume over time, with as little as 10% remaining after 1 year.\textsuperscript{23,24} Thus re-absorption of fat is also likely, causing loss of girth and, if not uniform, penile distortion.

In an attempt to provide a more uniform and persistent girth augmentation, combined grafts of dermis with attached fat have been placed between the twin graft beds of the dartos fascia and Buck’s fascia. The dermal surface of the graft is placed facing up towards the dartos for a smooth contour, and theoretically each side of the graft undergoes neovascularization from its respective fascial covering.

Harvest sites for these dermal grafts may be from the groin or bilateral gluteal creases. Grafts of 1.0cm thickness are considered ideal.\textsuperscript{15} The harvesting is more time-consuming and requires closure of the donor site, but graft-take and cosmetic appearance are considered to be superior. The graft is sutured at the corona and base of the penis and anchored on either side of the urethra, to avoid a fully circumferential graft that may contract and cause constriction. Placement of the graft may be achieved by inverting the penis through the infrapubic
incision used for penile lengthening; if only girth enhancement is desired, a circumferential incision below the corona is sufficient.

More recently, an alternative technique for girth enhancement has been undertaken by Austoni et al., described as corporoplasty augmentation surgery.\(^{25}\) Increase in the diameter of the erect penis is achieved by enlarging the albuginea of the corpora cavernosa, by means of bilateral venous grafts. The albuginea are incised longitudinally from the glans to the pubis, along the lateral aspect of each corpus cavernosum, and a saphenous vein graft is placed. Nine months postoperatively the increase in penile diameter in the erect state was between 1.1cm and 2.1cm (\(p<0.01\)) in the 39 patients reported. There was no significant increase in diameter of the flaccid penis.

**Theoretical risks**

No operation is without risk, especially when the technique is not standardized or described in the literature. In 1996, excellent descriptions of penile enlargement procedures were published by Alter, which allowed better understanding of the surgery and were intended to reduce the incidence of complications.\(^{15,23}\) Significant bleeding from the procedure is rare, although in 1992 a Miami lounge singer died after penile enlargement while on anticoagulation.\(^8\) Other potential risks of penile augmentation include infectious complications, downward deflection of the penis due to release of the suspensory ligament,\(^{26}\) resorption of fat grafts, and injury to the neurovascular bundle with resultant erectile dysfunction or penile numbness. Failure to increase penile length or girth is a notable possibility as well.

**Complications**

Rosenstein, in 1995, reported postoperative problems of pain, discharge, edema, dehiscence, flap loss, phimosis, paraphimosis, and infection. Long-term fat loss and encapsulation were also reported and, in 10% of patients, additional surgery was necessary.\(^{28}\) Another source of information on complications is reports of patients seen by other physicians after penile augmentation surgery.\(^{6,27}\)

Dissatisfaction with the cosmetic result is the most common complaint and may be due to lengthening or girth augmentation. These cases represent only a small percentage of men who have undergone penile augmentation; the denominator is unknown and thus a verifiable complication rate may never be available.\(^9\)

The most common complaint related to lengthening procedures is scrotalization of the penile shaft, in which the advancement of hair-bearing skin onto the penis after VY plasty leads to an undesirable result (Figure 52.3). The skin advancement can also lead to a picture of phimosis; circumcision should be undertaken with caution, since later reversal of the VY plasty may not be possible, owing to lack of shaft skin.\(^7\) A thick, hypertrophic scar, most prominent at the apex of the Y-plasty, is another frequent complaint (Figure 52.4). It is the authors' opinion that this relates to excess tension caused by inadequate mobilization of the lateral skin flaps rather than keloid formation. Wound infections requiring hospitalization, abscess formation, and wound separation also have been described.

Girth enhancement using autologous fat injection can lead to irregular residual fat nodules that cause patients to seek treatment (Figure 52.5). Some have undergone repeat ‘touch-up’ injections in an attempt to smooth the contour. Difficulty with intromission may occur, owing to excessive fat deposits on the shaft, as well as a decrease in shaft sensation over especially large nodules. Complete loss of the graft over time may occur.

Sexual function may be impaired by the development of erectile dysfunction (ED), loss of penile sensation as a result of neurological injury, painful erections, ventral penile deflection, or failure to address pre-existing ED.\(^9\)

**Results**

Interpretation of results is difficult, since most practitioners of penile enlargement do not use standardized techniques to measure length before and after surgery. Ideally, flaccid length from penopubic skin to meatus, stretched length, and erect length would be measured by a single observer. Rosenstein reported a mean increase in length of 2.1 inches (5.3cm), but he did not specify whether flaccid or erect and, most importantly,
Risks, complications, and outcomes of penile lengthening and augmentation procedures

Figure 52.4 Patients with poor cosmetic outcome of skin incision. (a) Hypertrophic scar. (b) Scrotal dog-ears and scrotalization incompletely reversed by the original surgeon. With permission from J Urol 1996; 156: 1617–20.

Figure 52.5 Patients with irregular deposition of autologous fat harvested with liposuction and injected into the penis. (a) Excessively broad base. (b) Nodule of fat caused by shifting in the early postoperative period. (c) Sonographic appearance of fat deposit. With permission from J Urol 1996; 156: 1617–20.
based measurements on photographs of the patients. Long reported a mean increase in length of 3.8 cm, but the measurements were taken in the operating room immediately after surgery, which makes their interpretation suspect. Bondil and Delmas preformed a study in cadavers and found that penile length after release of the suspensory ligament alone was increased by 0.5 cm, while addition of a skin advancement increased the gain in length to 1.6 cm.

Li et al. conducted a study in 42 patients undergoing division of the penile suspensory ligament between 1998 and 2005, which objectively assessed the increase in stretched penile length. The mean increase in stretched penile length was 1.3 ± 0.9 cm, and the only technique in which there was significant gain in length was that involving placement of a silicone buffer to prevent ligamentous re-attachment. In some motivated patients who performed postoperative stretching with penile weights, a vacuum constriction device, or a penile stretcher device a gain of up to 3 cm was achieved. The overall patient satisfaction rate was 35% but it was lower in the subgroup of 27 men (64%) with penile dysmorphic disorder.

Division of the suspensory ligament can certainly give the appearance of greater penile length, but often with only modest results. However, the increase in penile length achieved is often not to a degree that the patient finds satisfactory, and men with penile dysmorphic disorder often have unrealistic expectations.

Likewise, girth enhancement using autologous fat placement can increases penile circumference, but the exact amount of increase and durability are unproven. The technique of cavernosal augmentation with saphenous vein has given promising results for increasing erect penile diameter, but may be considered experimental and a somewhat invasive procedure and should not be preformed in men with 'locker room syndrome'.

To support the use of these procedures to increase self-esteem, a validated questionnaire should be developed to measure this construct and to show that penile augmentation increases self-esteem in a statistically significant manner.

**Correction of complications**

The two main complaints that lead patients to seek reversal of their penile augmentation are scrotalization of the penile shaft and irregular fat deposits. Since 1994, the authors have operated on 20 men to correct these complications, and Alter has reconstructed another 17 men. The successful correction of these penile deformities is very challenging, both from a technical point of view and because of the demanding nature of the patient population. These men have suffered disfiguring genital complications from surgery that they themselves requested. As a result, many have to resolve shame, guilt, and self-recrimination before they can seek help. Once it has been determined that the patient desires correction of the deformities, choosing the timing of the procedure becomes one of the key decisions for the surgeon. To avoid tissue ischemia and flap loss, the authors advise waiting at least 6 months until all the edema and induration has resolved.

Reversal of the VY plasty will usually correct scrotalization of the penis and any dog-ears. Patients should expect to lose any gain in length from the original operation, and if they are not willing to accept this risk the procedure should not be undertaken. Paucity of shaft skin may prevent a complete reversal, but in most men, opening up the full extent of the V incision allows mobilization and re-attachment of the apex of the flap, re-creating the inverted V (Figure 52.6). If penile deflection or instability has occurred, formal re-attachment of the tunica albuginea to the pubis should be performed with an

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*Figure 52.6* Reversal of deformity shown in Figure 52.3. (a) Incision through original scar. (b) Re-approximation of apex of flap into a V. (c) Final result after 3 months. With permission from J Urol 1996; 156: 1617–20.
absorbable suture. When the inferior skin flap is being advanced back up to the superior aspect of the Y, dermal sutures should be placed from beneath the flap to the pubis or Scarpa’s fascia in order to anchor the proximal aspect of the shaft skin, thus recreating the penopubic skin junction. A multilayer closure and closed suction drainage are recommended. Resection of irregular fat deposits should not be considered easy, since the fat is extremely adherent to the penile shaft skin. If care is not taken, the penile skin can be devascularized and may slough. Patients should be counseled that it may not be possible to remove all the fat in a single procedure, and that a staged approach may be indicated. If reversal of the VY incision is planned, the fat can be removed through that incision by inverting the penis. When fat excision alone is desired, a distal incision can be performed below the corona: a partial circumference incision may be preferable to retain as much collateral blood supply as possible.

Complications occur rarely with reversals. Of the authors’ 20 patients, one developed a hematoma and another developed significant induration and edema of the penile skin, which took 6 months to resolve; this was attributed to embarrassment of the skin circulation after resection of fat. After reported one hematoma and one inadequate reversal in 25 reconstructive operations.27

Conclusion
Penile augmentation techniques have been described in reputable publications, but supporting data to prove the effectiveness of these procedures are not impressive. No clear-cut indications have been developed, although guidelines for what is considered a normal adult penile length have been proposed.13,22

Division of the suspensory ligament is a straightforward technique that has been used along with other methods to increase penile length. Nevertheless, complications from skin advancement maneuvers are devastating to patients, who expect results without risk. Likewise, girth enhancement can increase circumference, but the simpler technique of autologous fat injection should be considered discredited at the present time. A significantly higher level of skill is needed to perform successful dermal-fat grafting or corporeal augmentation, but long-term and substantial data on this technique are not yet available.

Treatment of complications should be undertaken with caution, after allowing the existing wounds to mature, by reversal of the VY-plasty and resection of aberrant fat deposits.

Penile augmentation is an unregulated cosmetic procedure that is not reimbursed by insurance companies; nevertheless, it must be efficacious if it is to be performed. Comparisons between penile enlargement and breast augmentation are not appropriate, since breast augmentation, for all its potential risks, does increase the size of the breast in a statistically significant fashion. The results of penile lengthening and girth enhancement are unproven, whereas the complications are well described, implying that a risk–benefit analysis cannot be carried out. For these reasons, the authors consider penile augmentation to be still experimental.31

REFERENCES

16. Lue TF. Personal communication, 1995.
Peyronie’s disease: evaluation and review of non-surgical therapy

Frederick L Taylor and Laurence A Levine

Definition

Peyronie’s disease (PD) is a psychologically and physically devastating disorder that is manifest by a fibrous inelastic scar of the tunica albuginea, resulting in palpable penile scar in the flaccid condition and causing penile deformity, including penile curvature, hinging, narrowing, and shortening, and painful erections. In spite of multiple treatment options offered since François de la Peyronie described PD in 1743, this disorder remains a considerable therapeutic dilemma even to today’s practicing physicians.

Evaluation of the patient with Peyronie’s disease

Thorough evaluation of the PD patient is essential not only to diagnose the disease correctly, but also to guide treatment. Currently, no universally accepted standardized evaluation for PD exists, nor has a validated questionnaire been developed. A suggested guideline for initial evaluation of the PD patient, including history, physical examination, and imaging analysis, has been recommended and is outlined below.

The subjective assessment begins with the patient interview. History should be focused on the onset and duration of symptoms, the patient’s presenting signs and symptoms, and the presence or absence of pain. It is particularly useful to elucidate whether the patient continues to experience pain at the time of the initial evaluation, since this may represent a man in the acute phase of the disease. Pain may be present with palpation or erection or during coitus, and these settings should be differentiated since they may indicate different etiologies or degrees of acute inflammation. The patient’s subjective curvature deformity should be noted. It should also be noted that up to 90% of men with PD may present with diminished rigidity. In our experience, up to 50% of men with ED and PD have reported the onset of ED preceding PD. It is also important to know what, if any, prior PD therapies the patient has undergone, as this may help to guide future treatment. A detailed past medical and sexual history should be part of the initial evaluation of every man with PD. Medical history should focus on personal or family history of wound-healing disorders, including Dupuytren’s contracture, which is reported in up to 20% of patients with PD. Any risk factors for ED, such as dyslipidemia, hypertension, atherosclerotic disease, a history of tobacco use, and diabetes, should be queried. The patient’s baseline erectile function should be assessed using a validated questionnaire. Although a validated PD questionnaire is still in development, the International Index of Erectile Function (IIEF) may be used to gauge the patient’s baseline sexual function.

The objective evaluation begins with the physical examination. Although the focus should be on the genital examination, an examination of the hands and feet is appropriate given the patient’s history. Measurement of penile length is critical, since the loss of penile length is not only a known complication of PD, but is also a source of great concern among patients. The penis should be measured stretched in its flaccid state dorsally from pubis to corona or meatus. Note that the suprapubic fat pad should be compressed during measurement. Objective evaluation of curvature is best performed using penile duplex ultrasound after pharmacologic stimulation to produce a full erection equal to or better than the patient’s at home. Simple erection induction in the office will allow objective assessment of deformity. Duplex ultrasound will allow assessment of vascular flow rates, the degree of curvature as measured with a protractor, the presence and location of any Peyronie’s plaque (or plaques), and the presence of any hinge effect. In addition, plaque calcification can be assessed. Autophotography should not be used as the sole means for curvature measurement, as this modality can be inconsistent and inaccurate.

The final portion of the PD evaluation is objective assessment of the patient’s erectile capacity and penile sensation. During duplex ultrasound the patient should be asked to grade their pharmacologic erection compared with home erections. In addition, biothesiometry is recommended to assess penile sensation. Using the distal phalanx of the index fingers as positive control and the ventral surface of bilateral thighs as negative control, the point at which vibratory sensation is appreciated should be measured on the midshaft bilaterally and on the glans.

Non-surgical therapy for Peyronie’s disease

Since the first description of PD in the literature, physicians have been searching for medical therapy options with little
confirmed success. Consistent successful medical therapies continue to evade the practicing urologist, although current research into the molecular pathophysiology of PD may one day lead to a medical cure. Several non-surgical options, however, are currently available and may stabilize or reduce deformity and improve sexual function. The evaluation of their efficacy has been compromised by clinical trials that are small and, in most cases, without any placebo control. Data outcomes are difficult to interpret in the absence of a validated questionnaire, and in a disease in which spontaneous improvement has been noted in 5–12% of patients.5–6 Below, the non-surgical options for treatment of the pain and curvature of PD, including oral, topical, intralesional, external energy, and combination therapies, are presented (Table 53.1).

**Oral therapies**

**Vitamin E**

Vitamin E was the first oral therapy to be described for the treatment of PD.7 Vitamin E is a fat-soluble vitamin that is metabolized in the liver and excreted in bile and is thought to have antioxidant properties in humans. Oxidative stress and the production of reactive oxygen species (ROS) is known to be increased during the acute and proliferative phases of wound healing, since it is neutrophils and macrophages that produce these ROS, and the inflammatory phase of wound healing has been shown to be prolonged in patients with PD.9 Thus, a biochemical rationale does exist for vitamin E use. Gelbard et al. compared vitamin E therapy to the natural history of PD in 86 patients; no significant differences were found between the two groups in terms of curvature, pain, or the ability to have intercourse.9 In 1983, Pryor et al. performed a double-blind, placebo-controlled, crossover study evaluating vitamin E for the treatment of PD in 40 patients.10 No significant improvements were noted in plaque size or penile curvature. More recently, Safarinejad et al. published a double-blind, randomized trial of vitamin E with or without propionyl-L-carnitine (PLC) for the treatment of early PD. Patients were randomly assigned to receive vitamin E, PLC, vitamin E plus PLC, or placebo.11 No significant improvement in pain, curvature, or plaque size was noted in any active treatment group compared with placebo.11

In the opinion of the authors, vitamin E is not recommended for the treatment of PD since there is no evidence of benefit in placebo-controlled trials.

**Colchicine**

Colchicine is an anti-gout medication that inhibits fibrosis and collagen deposition primarily by inhibiting the inflammatory response through inhibition of neutrophil microtubules.12 Colchicine has been used both as primary oral therapy for PD as well as in combination with other modalities. Akkus et al. administered an escalating dose of colchicine in a non-randomized, non-placebo-controlled fashion to 19 patients with PD over a 3–5 month period.13 Thirty-six percent of the patients noted a reduction in curvature, and 63% noted an improvement in the palpable plaque. Seventy-eight percent of the patients who were experiencing painful erections at the time of treatment initiation had resolution of this symptom.

Kadioglu et al. treated 60 patients with PD using colchicine 1mg twice daily, with a mean follow-up of 11 months.14 They found significant improvement in pain in 95% of men; however, 30% of patients reported improved curvature while 22% of patients reported worsened curvature.14 Safarinejad performed a randomized, placebo-controlled trial of colchicine in 2004 with 84 men.15 It was found that colchicine is no better than placebo at improving pain, curvature angle, or plaque size as measured by ultrasound.

Colchicine is not recommended by the authors owing to its lack of demonstrated efficacy in placebo-controlled trials. The agent is also associated with gastrointestinal distress, including diarrhea, and rarely with aplastic anemia.

**Potassium aminobenzoate**

Potassium aminobenzoate is a member of the vitamin B complex that is believed to increase the activity of monoamine oxidase in tissues, thereby decreasing local levels of serotonin and thus possibly decreasing fibrogenesis. Potassium aminobenzoate is used for other conditions, including scleroderma, dermatomyositis, and pemphigus. Zarafonatis and Horrax first described the use of potassium aminobenzoate for the treatment of PD,16 and a subsequent European study published in 1978 reported a 57% improvement rate with 95% complete resolution in a pooled cohort of 2653 patients.17 This study, however, did not include a control or placebo group. In 1999, Weidner et al. published a randomized, placebo-controlled trial of potassium aminobenzoate 3g orally, four times per day for 1 year, in 103 men.18 The only significant difference found between the two groups was plaque size, which was not shown and has not been shown to correlate with a decrease in penile curvature. A 2005 follow-up study, also by Weidner et al., suggested that the use of potassium aminobenzoate may protect against progression of PD plaques.19 Potassium aminobenzoate is expensive, and has low tolerability owing to gastrointestinal side-effects. It is also not recommended by the authors because of a lack of evidence regarding its efficacy in the treatment of PD.

**Tamoxifen citrate**

Tamoxifen is a non-steroidal antiestrogen that acts by competing with estrogen binding sites in target tissues. In addition, tamoxifen affects the release of transforming growth factor (TGF)-beta from fibroblasts and blocks TGF-beta receptors, thus potentially reducing fibrogenesis.20,21 In 1992, Ralph et al. investigated tamoxifen in 36 patients with recent-onset PD (duration less than 4 months).22 Eighty percent of the patients reported a reduction in pain, 35% reported a subjective reduction in curvature, and 34% reported a decrease in plaque size. A follow-up study in 1999 by Teloken et al. failed to show any statistically significant difference between tamoxifen and placebo, and there was a reported increase of alopecia in the active treatment group.22

We do not recommend the use of tamoxifen.

**Carnitine**

Carnitine is a naturally occurring metabolic intermediate. Carnitine facilitates the entry of long-chain fatty acids into
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mechanism of action</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td><strong>Oral</strong></td>
<td></td>
<td></td>
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<tr>
<td>Vitamin E</td>
<td>Antioxidant that theoretically reverses or stabilizes pathologic changes in the tunica albuginea</td>
<td>Limited side-effects, low cost. Efficacy not proven</td>
</tr>
<tr>
<td>Colchicine</td>
<td>Inhibits fibrosis and collagen deposition through inhibition of neutrophil microtubules</td>
<td>Mixed reports of efficacy in non-controlled trials. Single randomized, controlled trial failed to show benefit. May cause gastrointestinal disturbances, including severe diarrhea</td>
</tr>
<tr>
<td>Potassium aminobenzoate</td>
<td>Member of the vitamin B complex, thought to increase the activity of monoamine oxidase, thereby decreasing local serotonin levels, which may contribute to fibrogenesis</td>
<td>Significant reduction in plaque size, but not curvature. Expensive, and difficult to tolerate due to gastrointestinal side-effects</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>May reduce release of transforming growth factor-beta from fibroblasts and may block transforming growth factor-beta receptors, resulting in diminished fibrogenesis</td>
<td>Efficacy not proven. Side-effects may include alopecia</td>
</tr>
<tr>
<td>Carnitine</td>
<td>Believed to inhibit acetyl co-enzyme A</td>
<td>Efficacy not proven, and more investigation is needed</td>
</tr>
<tr>
<td>l-Arginine</td>
<td>Amino acid substrate in the formation of nitric oxide, which is thought to be lacking in PD tissue</td>
<td>Improvement in plaque size and collagen–fibroblast ratio in a rat model. Well tolerated</td>
</tr>
<tr>
<td>Pentoxifylline</td>
<td>Non-specific phosphodiesterase inhibitor that may reduce collagen levels in PD plaques</td>
<td>Improvement in plaque size and collagen–fibroblast ratio in a rat model</td>
</tr>
<tr>
<td><strong>Topical</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verapamil</td>
<td>Increases extracellular matrix collagenase secretion and decreases collagen and fibronectin synthesis and secretion; decreases fibroblast proliferation</td>
<td>When administered topically the drug does not appear to penetrate into the tunica albuginea</td>
</tr>
<tr>
<td><strong>Intralesional</strong></td>
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<tr>
<td>Corticosteroids</td>
<td>Anti-inflammatory and cause reduction in collagen synthesis</td>
<td>Treatment with corticosteroids is discouraged by the authors. Effects are unpredictable, and may cause atrophy and distortion of tissue planes</td>
</tr>
<tr>
<td>Collagenase</td>
<td>Breakdown of collagen</td>
<td>Statistically significant improvement in curvature has been noted in men with mild-to-moderate disease</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Increases extracellular matrix collagenase secretion and decreases collagen and fibronectin synthesis and secretion; decreases fibroblast proliferation</td>
<td>Controlled and non-controlled trials show promise as improvements in plaque volume, pain, and curvature have been reported</td>
</tr>
<tr>
<td>Interferons</td>
<td>Decrease the rate of proliferation of fibroblasts in Peyronie’s plaques in vitro, reduce production of extracellular collagen, and increase production of collagenase</td>
<td>Recent encouraging results with reports of improvement in curvature and pain. Dosing regimens and side-effect profiles yet to be determined</td>
</tr>
<tr>
<td><strong>External energy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penile ESWT</td>
<td>ESWT-induced inflammatory response with resultant plaque lysis, improved vascularity, and the creation of contralateral scarring</td>
<td>No statistically significant improvement noted in curvature, plaque size, or pain</td>
</tr>
<tr>
<td>Electromotively administered verapamil with or without dexamethasone</td>
<td>Effect of verapamil and corticosteroids discussed above. Electric current itself may have some beneficial effect on wound healing</td>
<td>Objective improvements of plaque size and curvature have been noted. Adverse effects include erythema at electrode site</td>
</tr>
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(Continued)
Table 53.1 (Continued)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mechanism of action</th>
<th>Comments</th>
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<tbody>
<tr>
<td><strong>Combination therapy</strong></td>
<td></td>
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<tr>
<td>Vitamin E plus colchicine</td>
<td>Discussed above. Synergistic effect possible</td>
<td>Improvements in curvature and plaque size have been noted</td>
</tr>
<tr>
<td>ESWT with intralesional verapamil injection</td>
<td>Discussed above. Synergistic effect possible</td>
<td>Significant improvement in plaque size compared with placebo</td>
</tr>
<tr>
<td>Intralesional verapamil with oral carnitine or</td>
<td>Discussed above. Synergistic effect possible</td>
<td>Statistically significant subjective improvement in curvature, plaque size, and erectile function in patients treated with carnitine and intralesional verapamil</td>
</tr>
<tr>
<td>tamoxifen</td>
<td></td>
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<tr>
<td><strong>Penile traction devices</strong></td>
<td></td>
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</tr>
<tr>
<td>FastSize® penile extender</td>
<td>Chronic traction forces may trigger scar remodeling and formation of new connective tissue</td>
<td>Early results demonstrate reduction of curvature, increase in length, and improvement in hinge effect. Side-effects were limited to mild discomfort with the device</td>
</tr>
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PD, Peyronie's disease; E SWT, electroshock wave treatment

muscle mitochondria, which are then used as energy substrate. Carnitine is also thought to inhibit acetyl co-enzyme A, which may aid in the repair of damaged cells. Biagotti and Cavallini examined the use of carnitine for PD in 2001.\textsuperscript{22} Forty-eight men were divided into two groups to receive either tamoxifen 20mg twice daily for 3 months or acetyl-L-carnitine 1g twice daily for 3 months. Overall, the men taking carnitine saw greater improvement in curvature and had statistically significant improvement in pain. In addition, the patients taking carnitine reported far fewer side-effects than the patients taking tamoxifen.

More study is needed to elucidate the role of carnitine in the treatment of PD.

\textit{L}-Arginine

\textit{L}-Arginine is an amino acid that, when catalyzed by nitric oxide synthase (NOS), combines with oxygen ultimately to form nitric oxide (NO). It is known that inducible NOS (iNOS) is expressed in the fibrotic plaques of PD, and that long-term suppression of iNOS exacerbates tissue fibrosis.\textsuperscript{24} In 2003, Valente et al. reported that \textit{l}-arginine, given daily in the drinking water of a rat model with TGF-beta-1-induced PD plaques, resulted in an 80–95\% reduction in plaque size and in the collagen–fibroblast ratio.\textsuperscript{24} In addition, \textit{l}-arginine was found to be antifibrotic \textit{in vitro}. This suggests that \textit{l}-arginine, as a biochemical precursor of NO, may be effective in reducing PD plaque size.

Further human trials are needed before this agent can be strongly recommended.

Pentoxifylline

Pentoxifylline is a non-specific phosphodiesterase (PDE) inhibitor. Valente et al. found that normal human and rat tunica albuginea, as well as PD plaque tissue, express PDE-5A-3 and PDE-4A, PDE-4B, and PDE-4D.\textsuperscript{24} In their \textit{in vitro} study, PD fibroblasts were cultured with pentoxifylline and were found to have increased cAMP levels and reduced collagen levels compared with controls. In addition, pentoxifylline given orally to a TGF-beta-1-induced PD rat model resulted in decrease in PD plaque size and in the collagen–fibroblast ratio. Brant et al. reported a single case report of successful PD treatment using pentoxifylline alone.\textsuperscript{25}

Further studies are required to make a definitive examination of pentoxifylline for the treatment of PD; however its known biochemical effect and early animal-model success make it an attractive option for oral therapy.

**Topical therapies**

**Verapamil**

Interest in topical verapamil for the treatment of PD followed its success as an intralesional agent (see below). It does not appear, however, that tunica albuginea tissue concentrations of verapamil are achievable through topical application. In 2002 Martin et al.\textsuperscript{26} demonstrated that application of 0.5mg of a 40mg/ml verapamil gel to the penile shaft at 10 p.m. the night before and 5 a.m. the morning of scheduled PD surgery failed to result in measurable levels of the drug in the tunica albuginea. Of note, urine levels of verapamil obtained at the same time as the tissue samples did demonstrate verapamil concentration consistent with systemic absorption. A recent three-arm trial without a known placebo demonstrated benefit with topical verapamil,\textsuperscript{27} but this study was significantly compromised.\textsuperscript{28} Thus the use of verapamil as a topical agent for PD is not recommended.

**Intralesional therapies**

**Corticosteroids**

The powerful anti-inflammatory effect of corticosteroids led to their early investigation as agents for intralesional therapy of PD. In 1954, Bodner et al. reported improvement in 17 patients treated with intralesional hydrocortisone and
cortisone. In 1975, Winter and Khanna showed no difference between patients treated with dexamethasone injections and the natural history of the disease. In 1980, Williams and Green published a prospective study using intrallesional triamcinolone. All patients were observed for 1 year after study enrollment; during that time only 3% of patients reported improvement. Triamcinolone was administered every 6 weeks for 36 weeks; 33% of patients reported subjective improvement, particularly in pain and plaque size.

Currently, the use of intrallesional corticosteroids is discouraged because of the side-effects of local tissue atrophy, fibrosis, immune suppression, and lack of objective measures of benefit.

Collagenase

Collagenase was first studied in vitro by Gelbard et al. in 1982. A subsequent clinical trial by that group demonstrated subjective improvement in 64% of patients within 4 weeks of treatment. A decade after their initial study, they published their findings of a double-blind trial in 49 men. Statistically significant improvement in curvature was noted in the collagenase-treated group; however, maximal improvement ranged from 15°–20° and was only seen in the patients with curvatures of less than 30° and plaques of less than 2 cm in length. Larger-scale controlled trials of collagenase are currently in development.

Verapamil

Verapamil is a calcium-channel blocker that has been shown in in vitro studies to inhibit local extracellular matrix production by fibroblasts, to reduce fibroblast proliferation, to increase local collagenase activity, and to affect the cytokine milieu of fibroblasts. In 1994, Levine et al. reported on 14 men who underwent a dose-escalation trial of intrallesional injections of verapamil every other week for 6 months. Significant improvement in plaque-associated narrowing was noted in all patients, and curvature was improved in 42%.

The first randomized, single-blind trial of intrallesional verapamil was published in 1998. Significant differences were noted in terms of erection quality and plaque volume. A trend towards improvement in curvature was also noted. As a follow-up, Levine and Estrada reported on 156 men enrolled in a prospective non-randomized trial of PD men with a mean follow-up of 30.4 months. A local penile block was performed with 10–20 ml bupivacaine 0.5%, followed by injection of verapamil 10 mg diluted in 6 ml sterile normal saline (total volume 10 ml) into the Peyronie’s plaque using between one and five skin punctures, but with multiple passes through the plaque. The goal is to leave the drug in the needle tracks but not to tear or disrupt the plaque. Injections were administered every 2 weeks for a total of 12 injections. Eighty-four percent of patients with pain achieved complete resolution, 62% were found on objective measurement to have improved curvature ranging from 5° to 75° (mean 30°), and only 8% of patients had measured worsening of curvature.

More recently, Bennett et al. administered six intrallesional injections (verapamil 10 mg in 5 ml) every 2 weeks to 94 consecutive patients with PD. Follow-up was at an average of 5.2 months after completion of the sixth injection. Eighteen percent of patients (n = 17) were found to have improved curvatures (average improvement 12°), 60% (n = 56) had stable curvature, and 22% (n = 21) had increased curvature (average increase 22°). All patients with pre-treatment penile pain had improvement at follow-up. The authors suggest that these data support intrallesional verapamil for the stabilization of PD.

It may be that six injections provide stabilization but are insufficient to accomplish reduction of curvature. Currently, we recommend a trial of six injections, with injections occurring at 2-week intervals. If no improvement is noted by the patient, the therapy may be terminated, the verapamil dose can be increased to 20 mg, or interferon injections may be offered. If improvement is reported, another six injections are given. We consider verapamil to be contraindicated in patients with ventral plaques or extensive plaque calcification.

Interferons

Duncan et al. reported in 1991 that interferons decrease the rate of proliferation of fibroblasts in Peyronie’s plaques in vitro, reduce the production of extracellular collagen, and increase the activity of collagenase. Initial studies performed by Wegner et al. demonstrated low rates of improvement, but a high incidence of side-effects, including myalgias and fever. In 1999, Ahuja et al. reported on 20 men who received 1 × 10⁶ units of interferon-alpha-2b every other week for 6 months. One hundred percent of patients reported softening of plaque, 90% of men presenting with pain had improvement, and 55% had a subjective reduction in plaque size. Dang et al. administered 2 × 10⁶ units to 21 men, twice weekly for 6 weeks and found objective curvature improvements in 67%, and improvement in pain in 80%. Seventy-one percent of patients reported improvement in ED symptoms. In 2006, Hellstrom et al. reported on a placebo-controlled, multicenter trial of 117 patients who underwent injections of 5 × 10⁶ units every other week for a total of 12 weeks. Average curvature in the treatment group improved by 13° compared with 4° in the placebo arm, and 27% of patients in the treatment group had measured improvement compared with 9% of the saline group. Pain resolution was noted in 67% of the treatment patients compared with 28% of the placebo group.

Interferon therapy requires further investigation to determine adequately its efficacy, dosing regimens, and side-effect profiles before its routine use in PD patients can be recommended.

External energy therapies

Penile electroshock wave therapy

Local penile electroshock wave therapy (ESWT) has been suggested to be helpful. Various hypotheses about its mechanism of action exist, including direct damage to the plaque resulting in an inflammatory reaction with increased macrophage reaction leading to plaque lysis, improved vascularity resulting in plaque resorption, and the creation of contralateral scarring of the penis resulting in ‘false’ straightening. Hauck et al. randomized 43 men to ESWT or oral placebo for
6 months.48 No significant effect was noted in terms of curvature, plaque size, or subjective improvement in sexual function or rigidity. More recent work from a German group randomized 102 men to ESWT or to receive sham shocks.49,50 There was no statistically significant difference found between the groups for plaque size, improvement of deformity, or sexual function post-treatment. ESWT is not currently recommended as therapy for PD.

Iontophoresis
Iontophoresis involves the transport of ions through tissue by means of an electric current. Several studies have investigated the efficacy of topically applied verapamil with or without dexamethasone with enhanced penetration using iontophoresis.51-54 In 2002, Levine et al. confirmed that verapamil was found within the exposed tunica albuginea by examining surgically retrieved tunica albuginea from patients after a single intra-operative exposure during plaque incision and grafting surgery.55 Di Stasi et al. recently reported on a prospective, randomized study of 96 patients treated with verapamil 5mg plus dexamethasone 8mg using iontophoresis versus lidocaine 2% delivered electromotively.56 Forty-three percent of patients in the verapamil–dexamethasone group noted objective improvement in plaque size and curvature; no changes were noted in the lidocaine group. In 2005, Greenfield et al. reported on the use of verapamil 10mg versus saline iontophoresis.57 Patients were assessed using papaverine-induced erections prior to and 1 month after treatment. Sixty-five percent of patients in the verapamil group demonstrated improvement in curvature compared with 58% in the saline group. Mean curvature improvement was 9.1° in the treatment group compared with 7.6° in the saline group,58 which is clearly not as robust a response as reported with intralesional verapamil injections. The authors suggested that the electric current itself may have some beneficial effect on wound healing, which is known and supported in the dermatologic literature.59 Investigation into iontophoresis is ongoing.

Combination therapy
Vitamin E and colchicine
A placebo-controlled study by Preito Castro et al. randomized 45 patients to receive vitamin E plus colchicine or ibuprofen.58 Statistically significant improvements in curvature and plaque size were noted in the group treated with vitamin E plus colchicine compared with the group receiving ibuprofen. Patients in the vitamin E plus colchicine arm reported a greater decrease in pain, although this did not reach statistical significance.

Penile electroshock wave therapy with intralesional verapamil injection
In 1999, Mirone et al. prospectively examined two groups of PD patients; one group was treated with ESWT, while the other received ESWT plus perilesional verapamil injections.59 A 52% improvement in plaque size by ultrasound was noted in the ESWT-only group compared with 19% in the combination-therapy group.59 A follow-up study by the same investigators involving 481 patients demonstrated a 49% improvement in plaque size among those treated with the combined therapy.60

Intralesional verapamil with oral carnitine or tamoxifen
In 2002, Cavallini et al. randomized 60 men to receive intralesional verapamil plus oral carnitine or intralesional verapamil plus oral tamoxifen.61 Statistically significant subjective improvements in curvature, plaque size, and erectile function were found in the carnitine group. No difference in improvement of pain was found between the two groups.

Penile traction devices
The use of tissue expanders has long been a mainstay of treatment in the orthopedic, oral–maxillofacial, and plastic surgical fields. It is well documented that gradual expansion of tissue results in the formation of new bone and connective tissue. Recently, initial work has been done to evaluate the efficacy of a penile extender device for the treatment of PD. A pilot study of 10 patients at our institution found that daily application of the FastSize Medical device for 2–8 hours per day for 6 months resulted in a 33% measured improvement in curvature (ranging from 10° to 45° improvement and resulting in an improvement in average curvature from 51° to 34°), an increase in flaccid stretched penile length ranging from 0.5cm to 2.0cm, and an improvement in hinge effect in all those with advanced narrowing or indentation. No patients noted recurrence or worsening of curvature during 6 months of follow-up, and there was no incidence of local skin changes, ulceration, loss of sensation, or worsening of curvature. Long-term and larger studies are indicated.52

Conclusion
PD remains a treatment dilemma, in part owing to the lack of a clear understanding of its pathophysiology. It is hoped that, with further basic science research and properly conducted clinical trials, novel treatments will emerge. Currently we do not believe that oral therapy alone provides any real benefit with respect to correction of deformity, since it appears unlikely that an adequate concentration of any agent will reach the relatively hypovascular and hypocellular plaque, and placebo-controlled trials have not demonstrated benefit. On the other hand, injection of verapamil or interferon-alpha-2b has been shown to provide, at a minimum, stabilization of plaque and deformity progression, and it may improve sexual function as well. The newest non-invasive, non-surgical treatment with prolonged traction poses a novel approach based upon proven principles of tissue remodeling, and there have been encouraging preliminary results. We feel that it is possible to achieve a synergy with combination therapy using medical treatment (oral and injection) with its potential chemical effects, and the mechanical effects of traction therapy. This combination may result in the best chance for a non-surgical reduction in deformity with improvement in sexual function. Further studies will clearly be necessary.
REFERENCES

1. La Peyronie F. Sur quelques obstacles qui s’opposent à l’éjaculation naturelle de la sémence. Mem Acad Royale Chir 1743; 1: 337–42.


Introduction

Peyronie’s disease (PD) is an incurable chronic condition that affects middle-aged men and often results in penile deformity with loss of coital function. Scar-like plaques form between layers of the thick fibrous tunica albuginea, often as a result of coital trauma. These plaques may result in penile curvature, hour-glass deformity, and erectile dysfunction (ED) caused by veno-occlusive incompetence, or they may be asymptomatic. The condition occurs in approximately 3.2% of men over age 40. Caucasians are at highest risk and the mean age is 57.4 years.¹ Presentation includes penile pain with erection, ED, inability to have intercourse secondary to penile deformity, and a palpable plaque. The putative etiology of PD is coital trauma to the penis with subtunical bleeding and inflammation, ultimately leading to fibrosis of the tunica albuginea, usually in the dorsal aspect. This fibrosis produces dense scar or plaque formation.²

Non-surgical treatment for PD has included oral medications, topical agents, intralesional injections, extracorporeal shockwave lithotripsy, and ultrasound.³ Most patients prefer non-surgical intervention prior to selecting a surgical procedure despite the small number of successes with medication. Ultimately treatment is designed to improve coital function and result in satisfactory, comfortable erection for both patient and partner.

Surgery for Peyronie’s disease

PD improves and even resolves spontaneously in fewer than 13% of men, progression is seen in 40%, and no change in 47%.³ Surgery is recommended for patients with stable PD and poor coital function. PD includes both an active and stable phase. The active phase occurs with the onset of PD and follows closely the traumatic event. Many men, however, do not recall specific trauma. The early, active phase lasts 12–24 months and is often characterized by painful erections, a changing plaque, and the development of penile curvature or other deformity during erection. The later, quiescent or stable phase is characterized by stable penile deformity, resolution of penile pain, and in some men the onset of ED. Surgery should be avoided during active plaque change, since the penile deformity changes and may resolve enough for some men to resume normal coital function. Montorsi et al. recommend waiting at least 12 months from the stabilized PD before considering any surgery.⁵ They suggest that many men with stable disease for less than 6 months may have curvature recurrence postoperatively.

The choice of a surgical procedure depends upon patient needs and preferences (Figure 54.1) Counseling of patients should be based on the function and type of penile deformity and quality of erection. Three surgical categories are used for PD patients:

- tunica lengthening procedures;
- tunica shortening procedures; and
- implantation of penile prosthesis with or without modeling.

Penile prosthesis implantation is reserved for men with Peyronie’s disease and refractory ED or men who prefer this method of treatment. Men with satisfactory erectile function with or without supportive medications are candidates for straightening procedures using either tunica lengthening or shortening operations. Tunica shortening procedures include plication techniques such as the Nesbit or Kelami procedures, and tunica lengthening procedures include plaque incision or excision and grafting such as the Horton–Devine operation.

Patient evaluation for surgery

Evaluating a patient’s erectile status is important in selecting appropriate surgical alternatives. Potency may be determined by sexual history, a PDE-5 inhibitor take-home test, a phosphodiesterase (PDE) type 5 inhibitor, or intracavernosal injection or Doppler ultrasound examination. Patient photographs may also be helpful in counseling patients before surgery. A strong history of rigid erections is one of the best determinants for choosing to proceed with a straightening procedure. Because many men with PD have avoided coitus for many months, they are uncertain of their potency. Indeed, severe curvature may preclude intromission and patients may not appreciate the quality of their erection or the presence of veno-occlusive dysfunction. In these men, a home trial of PDE-5 inhibitors with sexual stimulation and subsequent follow-up history of the quality of erections is helpful in choosing the best surgical procedure for the individual patient. When erection quality is still unclear or ED is likely, Doppler
Tunica lengthening procedures are best chosen for men with good erectile function, penile shortening, curvature of >45°, or hour-glass deformity. Tunica shortening procedures succeed most often in men with good erectile function, adequate penile length, or curvature of <45°. Figure 54.1 shows the algorithm for selecting treatment for Peyronie’s disease. Penile prosthesis implantation is best chosen for men with poor or absent erections or because of patient choice.

Preoperative counseling should include discussions of the patient’s and partner’s expectations, alternatives, treatments, and the risks, complications, and potential outcomes of surgery. The most frequent complications of straightening procedures include: penile shortening, glans hypoesthesia, ED, recurrent curvature, hematoma, and graft contraction.
Most patients will require the use of a PDE-5 inhibitor postoperatively for penile rehabilitation.

Tunica shortening

Plication procedures

The Nesbit procedure was first described in 1965 for correcting congenital penile curvature caused by corporal disproportion. Pryor and Fitzpatrick first reported its use in the treatment of patients with PD. Plication procedures require that the tunica opposite the Peyronie plaque and penile curvature is excised or plicated (or both) in order to straighten the penis. After an artificial erection is obtained with normal saline using the Gittes technique or with injection of a vasoactive agent into the corpora cavernosum, an initial circumcising incision is created followed by degloving of the penis to the location of maximal curvature. A ventral penile incision may be used for ventral exposure in very proximal dorsal curvature. Longitudinal penile shaft incisions should be avoided because postoperative scarring may be painful or unsightly or even produce further curvature. Buck’s fascia is dissected from the tunica albuginea in patients with dorsal curvature, or it is dissected off the dorsal neurovascular bundles for ventral curvatures. An artificial erection is induced and the point of maximum curvature is marked on the convex side of the penis. A 5–10mm transverse ellipse on the tunica albuginea may be excised in the classic Nesbit procedure (approximately 1mm for every 10° of curvature).

Rehman et al. modified this technique by using a partial-thickness shaving of the tunica to avoid possible bleeding and cavernosal injury. Alternatively, a longitudinal incision can be carried out at the location of the curvature and closed horizontally in the Heinike–Michalczwicz fashion.

Next, the tunica is closed ‘water-tight’ and horizontally using interrupted or running, locking, non-absorbable, braided sutures with buried knots. Non-absorbable sutures are preferable for maintaining correction during healing, as absorbable sutures are more likely to break, causing recurrence of curvature. A circumcision is recommended in men with redundant foreskin, owing to the increased risk for preputial edema, postoperative phimosis, or preputial necrosis. An artificial erection is again induced and, if the penis is straight, Buck’s fascia and the skin are closed. If extensive dissection has been required, a small subcutaneous drain such as the TLS drain may be used for 12–24 hours to diminish edema. If not adequately straight, subsequent plications or tunica incision or excision and closure are necessary.

A penile block is administered using long-lasting bupivacaine and a non-pressure dressing and an ice pack are applied. Patients may be discharged home on the same day after this operation. They should avoid sexual activity for 6 weeks.

Yachia modified the Nesbit procedure, making single or multiple 1–1.5cm longitudinal incisions along the convex side of the tunica, which are subsequently closed horizontally, applying the Heinike–Mikulicz principle. Yachia felt his modification would reduce injury to the neurovascular bundle and so reduce glans hypoesthesia, though this complication is still possible.

The author of this chapter prefers a longitudinal incision with horizontal closure in the Heinike–Mikulicz technique because tunical deformities and palpable suture lines appear to be fewer. Planning the tunical incision is facilitated by placing an Allis clamp to straighten the penis before performing the incision. Licht and Lewis compared the Nesbit, modified Nesbit, and tunical incision with grafting and found the highest satisfaction rates (83%) and lowest ED rates (0%) with the modified Nesbit procedure. Recent studies show patient satisfaction rates for the Nesbit procedure of 75–88% and rates of complete straightening of 61.9–82.1%. Similar rates of satisfaction (78–83%) and straightening (93%) have been found with Yachia’s modification to the Nesbit procedure.

Despite these high satisfaction and successful straightening outcomes, penile shortening remains difficult with the Nesbit, modified Nesbit, and other plication procedures. In a study involving 359 men, Pryor reported shortening of >1cm in 86.6% of men, between 1–2cm in 8.6% of men, and >2cm in 4.7% of men. Similarly, in another large study of 157 men with PD, Savoca et al. reported shortening of <1.5cm in 86%
of men and of 1.5–3 cm in 14% of men. Pryor suggests that the degree of penile shortening rarely precludes sexual activity, only occurring in 1.7% of men in his study. Analysis of other studies shows that the range for reported sexual dysfunction secondary to shortening is 1.3–11.9% for the Nesbit and modified Nesbit procedures. Complications with the procedures include curve recurrence (7.7–10.6%), ED (0–22.9%), penile indurations or narrowing (0–16.7%), suture granuloma (0–1.9%) and glans hypoaesthesia (0–21.4%). Glans hypoaesthesia is common postoperatively, though it frequently resolves after several months.

Tunica albuginea plication

Plication of the tunica albuginea is the least invasive technique for correction of PD, and it is often performed using only local anesthetic. Gholami and Lue describe a 16-dot plication method using multiple plication sutures with a high patient satisfaction rate. Following induction of an artificial erection, a ventral longitudinal or circumcising incision is performed. Longitudinal incisions are reserved for uncircumcised men desiring to keep their foreskin and are best carried out on the ventral aspect of the penis. Buck’s fascia is incised medial to the neurovascular bundle and an intravascular space developed bluntly between the dorsal vein and arteries. Nerve fibers travel lateral to these dorsal arteries, and plication sutures may be placed in the developed space. For men with a dorsal curvature, a ventral longitudinal incision is made down to Buck’s fascia overlying the corpus cavernosum.

After the center of the curve and entry and exit sites for the plicating sutures have been marked, sutures are placed 2 mm lateral to the corpus spongiosum. Two or three pairs of 2–0 braided permanent polyester sutures are placed through the tunica albuginea (four entry and exit points per suture). Van der Horst et al. found that polytetrafluoroethylene sutures result in significantly less patient complaints of discomfort than polypropylene sutures (13% vs 52%) when a similar plication technique is used. The sutures are gradually tied with one surgical knot placed and subsequent clamping. Once all plications are partly tied and clamped, the erect penis is examined. If the penis is straight using another artificial erection, the knots are completed and buried, ideally under minimal tension. The Buck’s fascia is then re-approximated with absorbable suture, and the skin closed.

A penile block is administered with bupivacaine, a non-compressive dressing, and an ice pack is applied. Patients may be discharged on the same day of surgery.

Gholami and Lue report that 85% of patients maintained a straight erection while 15% suffered curve recurrence in a study of 124 patients at a mean follow-up of 2.6 years. Forty-one percent of patients in their series reported shortening (from 0.5 cm to 1.5 cm), causing sexual dysfunction in 7% of patients. Twelve percent reported bothersome knots, 11% erectile pain, 9% penile indentation, 6% glans hypoaesthesia, and 6% worsened ED. Results vary for plication procedures, with straightening rates ranging from 57% to 85% and satisfaction rates ranging from 58% to 82%. Cahall et al. reported significantly poorer outcomes than Gholami and Lue, with 57% of patients reporting deterioration in their quality of life, 55% severe penile shortening, 48% glans hypoaesthesia, and 34% bothersome suture knot nodules.

Tunica lengthening procedures

Plaque incision or excision with placement of grafts has been used successfully for patients with severe penile curvature, for complex or hour-glass deformity, and in men with a shortened penis from PD. In 1950, Lowsley and Boyce first reported a series in patients with PD who underwent plaque excision with a fat graft, but there was no report of success.

Various materials have since been used including dermis, temporalis fascia, vein, cadaveric or bovine pericardium, dura mater, synthetic material, and porcine small intestine submucosa (SurgiSIS®). The ideal graft should be pliable, easy to handle, and packaged in various sizes, have good tensile strength, a low inflammatory response, a low patient morbidity, a low risk of disease transmission, and low cost.

The author prefers porcine SurgiSIS® Biograft (Cook Urological, Spencer, IN). SurgiSIS® is processed into a reliably packaged, acellular matrix, consistent in thickness and compliance. One drawback to the use of SurgiSIS® is that some religions may not accept a porcine graft material and patients should be made aware of the origin of the graft material. While some surgeons have had less satisfactory results, my experience with SurgiSIS® has been equivalent to or exceeded that with other grafts.

Synthetic materials, such as Dacron and Gore-Tex, may cause severe postoperative inflammation leading to fibrosis and post-correction curvature. Licht and Lewis reported poor patient satisfaction with synthetic grafts. Sampaio et al. report that 95% of men achieved a straight penis using cadaveric dura mater; however, this material has not been widely accepted because of concerns for prion and slow virus transmission. Cadavaric pericardium has been widely used with good postoperative results and excellent intra-operative tissue handling. Although prion transmission is rare, the media have increased the concern regarding cadaveric human tissues and prion transmission. Use of vein grafts is well documented.
with good results ranging from 60% to 95% in terms of straightening and from 88% to 92% in terms of satisfaction,\textsuperscript{4,28–31} although these procedures carry the risk of harvest site infection and lymphatic leak and they require longer operative time. Previously, deep dorsal penile vein has been used, but more recently vein grafts have used saphenous vein. Use of vein requires creation of a patchwork graft to fill larger tunical defects. Although I prefer SugiSIS\textsuperscript{5}, no material has emerged as the clearly superior graft.\textsuperscript{39}

The incision–excision straightening procedure begins with an artificial erection to assess penile curvature, as previously described. For dorsal plaques, a circumcising incision and degloving of the penis is performed. Ventral plaques may be accessed via a circumcising or a direct ventral incision longitudinally over the plaque. Dorsal penile incisions should be avoided. The neurovascular bundles, located lateral to the deep dorsal vein of the penis, should be carefully dissected off the underlying tunica albuginea. The plaque can be approached through the bed of the deep dorsal vein with venous ligation 1 cm proximal and distal to the maximum curvature. The deep dorsal vein is excised between these ligatures. Buck’s fascia can also be incised at the 3 o’clock and 9 o’clock positions and dissected off the tunica albuginea to retract the neurovascular structures from the plaque and curvature. Buck’s fascia and the contained dorsal penile nerves are then carefully dissected off the tunica albuginea using sharp dissection. A relaxing “H-shaped incision is then made in the plaque with subsequent grafting, a technique described by Lue and El-Sakka.\textsuperscript{40} Egydio describes an incision using “tripod-shaped forks of 120°” to produce a geometrically optimal relaxing tunical defect for easy graft suturing.\textsuperscript{41} This incision may also be termed a ‘Mercedes–Benz incision’ and it provides enhanced curvature correction for severe curvature, especially if associated with an hour-glass deformity at the location of the curvature.

Larger or calcified plaques may require complete excision. The measurement of graft size can be estimated by measuring the convex and concave portions of the erect penis and using the difference for the first graft size estimate. After the curvature has been incised or the plaque excised, measurements are taken from the corners of the tunical incision. It is important to raise flaps of tunica at the H- or Y-shaped incision to allow for full straightening.

The chosen graft material is cut approximately 20% larger than the measured defect and sutured to the tunica albuginea with a running locking 4–0 polyglycolic acid suture (PDS). Suture placement takes up approximately 3–5 mm of graft size on each side. Tisseal® (Baxter Healthcare, West Lake Village, CA) can be applied by spray under the graft for further adherence of the graft material to the underlying corporal tissue. After the graft has been sutured in place and Tisseal® applied, an artificial erection is induced to check straightening and, when necessary, plications are placed on the contralateral side of the penis to correct any residual curvature. Large residual curves may require a second incision and grafting. After straightening has been achieved, Buck’s fascia and the skin are closed.

A penile block is injected, a fine suction drain is kept beneath the skin overnight, a non-compression dressing is applied, and the patient is discharged that day or the following morning. Ice is maintained on the operative site for 48–72 hours.

Patients are discharged home on nightly diazepam for 2 weeks following surgery to prevent nocturnal erections, and amyl nitrite may be used as needed to prevent erections for that same period. Patients are advised to avoid sexual activity for 6 weeks following surgery for adequate healing. If patients experience mild curvature recurrence in the postoperative period, a vacuum erection device (VED) may be employed for 10 minutes twice daily without the constriction ring once the patient has recovered from the discomfort of surgery. This postoperative VED use is successful for mild-to-moderate curvature. Many patients will require a phosphodiesterase (PDE) type 5 inhibitor for 3–9 months after surgery to assist with ‘penile shock’ from surgery.

Reported satisfaction and straightening rates vary widely. Complications include worsening ED, with most studies reporting 0–15%,\textsuperscript{6,12,28–36} though this often takes up to 6 months to improve and may require assistance with a vacuum device or PDE-5 inhibitors. Since this ‘penile shock’ is expected in most patients, the author uses a PDE-5 inhibitor for 6–9 months following surgery. Other complications include penile shortening (0–40%), glans and penile hypoesthesia (0–16.7%), curve recurrence (0–16.7%), and hematoma.\textsuperscript{6,12,28–36}

Although the risk for increased penile shortening is less with these procedures than with plication procedures, patients still need to be warned of this outcome. PD itself will cause shortening and may increase this complaint. Yurkanin reported average penile lengthening of 2.1 cm in the flaccid penis in men with PD.\textsuperscript{8} Interestingly, over half the patients in this study reported subjective shortening.

**Penile prosthesis implantation**

Severe ED and PD is best treated with implantation of an inflatable penile prosthesis. The tunica lengthening and shortening procedures discussed above may provide a straight penis, though a complete loss of erectile function will result from surgery in some patients.

Montorsi et al. found that implantation of a semi-rigid prosthesis in men with PD had very poor 5-year patient (48%) and partner (40%) satisfaction rates despite a high satisfaction.
rate (90%) at 3 months. Complaints included poor erection quality and girth with erections, unnatural sensation, and partner pain. Meanwhile, these and other authors report good results with inflatable penile prosthesis, with patient satisfaction rates ranging from 75% to 93%.

Following penile prosthesis implantation, patients with continued curvature should be treated with modeling, plaque incision and grafting, or a modified Nesbit procedure. Wilson and Delk first described modeling in a large, 138-patient retrospective study. Prior to pump placement in the scrotum, the cylinders are distended maximally and the connector tubing to the pump is clamped to prevent excessive back-pressure. Additionally, digital pressure is placed over the corporotomy incisions to protect the suture lines. The penis is bent manually directly opposite the curve for 90 seconds. This results in plaque splitting and often an audible crack. Wilson and Delk reported this technique as being successful in 118 of 138 patients, avoiding plaque incision and grafting. They also reported that modeling was associated with greater postoperative pain and swelling and was possibly related to urethral perforation in four patients. Carson described the technique in 30 patients, 28 of whom suffered no complications from modeling and all of whom had good penile straightening at a mean follow-up of 31.4 months. The remaining 2 patients in this study required plaque incision and grafting. Chaudhary et al. reported the use of modeling in 28 of 46 patients undergoing prosthesis implantation for PD. The remaining 18 patients achieved adequate straightening merely with the prosthetic implantation. Furthermore, a recent study showed slightly higher patient (88% vs 81%) and partner (80% vs 72%) satisfaction rates for modeling compared with corporealplasty with insertion of inflatable penile prosthesis. AMS 700CX InhibiZone™ (American Medical Systems, Minnetonka, MN) and Coloplast Titan© (Coloplast, Minneapolis, MN) prostheses are best suited for patients with PD since these higher-pressure cylinders provide adequate rigidity to straighten the penis across the Peyronie’s plaque. AMS Ultraflex cylinders are less likely to provide adequate platform for modeling.

Complications of inflatable penile prosthesis implantation, such as infection and device breakdown, are no more common in men with PD than in others undergoing penile prosthesis implantation. As mentioned above, 4 of 138 patients in Wilson and Delk’s study suffered urethral perforation, possibly linked to modeling, though none of the patients in Carson’s or Chaudhary’s series experienced urethral injury. Regardless, all men undergoing prosthesis implantation should be warned before surgery of the risks for infection, device malfunction, urethral injury, penile shortening, and recurrent curvature.

**Conclusion**

Peyronie’s disease is an incurable, sexually debilitating disease resulting in penile deformity, coital failure, and significant psychological stress for many men and their partners. Urologists have an opportunity to help men suffering from PD to improve their lives and the lives of their partners.

Appropriate treatment should be individualized and tailored to the patient’s expectations, disease history, physical examination findings, and erectile function. After medical therapy is considered and the PD has stabilized, surgical correction is an excellent option for patients with functional impairment from their PD. Outcomes are excellent, with expected return to normal sexual function following PD treatment.

**REFERENCES**

Introduction

Priapism is a pathological penile erection that persists in the absence of sexual stimulation. It is a relatively poorly understood condition and is a medical emergency if ischemic, because of its attendant pain and the associated complication of permanent erectile dysfunction (ED). Despite significant advances in the understanding of the physiology of normal erection and pathophysiology of ED, the infrequent occurrence of this condition, the paucity of basic research, and the lack of controlled trials of therapeutic options has led to priapism being considered an enigma.

History

The term ‘priapism’ is derived from Priapus, one of the many mythological characters in Greek history. Modern medical awareness of the condition can be safely attributed to Hinman, who, in an article in 1914, described the condition as a thrombosis of the corporal veins and further attempted to describe the etiology as arising out of mechanical or nervous causes. He believed the majority of cases were due to mechanical causes resulting either from local factors (such as pelvic infections, perineal injuries and penile tumors), or from blood dyscrasias. These descriptions remain valid even today.

Epidemiology

The incidence of priapism varies depending upon the population being studied. Eland et al. reviewed the data of all men enrolled with the Integrated Primary Care Information database in the Netherlands. This study of 145,071 males with 341,133 person-years of follow-up is one of the most comprehensive epidemiologic publications for this condition. They reported an overall incidence of 1.5 cases per 100,000 person-years with an increase to 2.9% in men above 40 years of age. Intracavernosal therapy for ED was attributed to 0.6 per 100,000 person-years. This incidence is higher than the 0.34–0.52 per 100,000 persons reported by Kulmala et al. from Finland, and this may be due to the increased use of intracavernosal therapy for ED. There are further variations in the incidence depending on the ethnicity and prevalence of certain underlying medical conditions such as sickle cell disease, in which the incidence may be as high as 42%.

Priapism is principally classified into two types: low-flow priapism and high-flow priapism. This classification is based on the status of arterial flow into the corpora cavernosa during the priapic state and is instrumental in deciding the management strategy.

Low-flow (ischemic) priapism

Ischemic priapism is the more common of the two types of priapism. This is characterized by a low or absent blood flow into the penis along with pain in acidic corpora. The principal abnormality is an imbalance between arterial inflow and venous outflow from the penis. Persistent inflow with a decreased outflow leads to accumulation of blood within the cavernosal sinusoids along with progressively increasing tissue pressure. As the pressure rises, it may approach or surpass the systolic arterial pressure, with subsequent stasis of pooled blood resulting in hypoxia and acidosis. The condition is similar to a compartment syndrome.

Pathogenesis

Priapism is a phenotypic manifestation of an underlying dysfunction of normal cavernosal enzymes and proteins. Champion et al. conducted a series of experiments using transgenic mice with deficiency of endothelial nitric oxide synthase (eNOS) and neuronal NOS (nNOS) in varying combinations to evaluate their tendency for priapism. They found increased episodes of priapism in mutants homozygously negative for eNOS. This was associated with a decrease in the activity of phosphodiesterase (PDE)-5A protein. They concluded that mice deficient in eNOS could not break down the cGMP released after stimulation of the cavernosal nerve because of decreased activity of PDE-5, and eNOS restoration could reverse this trend. This whole phenomenon may be the result of super-sensitization to cGMP after an erectile stimulus. The same group further evaluated the role of Rho-kinase in the causation of priapism and noted decreased RhoA–Rho kinase-mediated contraction of the cavernosal smooth muscle cells in eNOS deficient mice.

This combination of increased excitatory neurotransmitters along with decreased contractile response may be the cause of priapism in a number of patients. Tissue hypoxia seems to be the principal factor responsible for the morbidity associated with ischemic priapism and has been the focus of research into the pathogenesis of this condition. Accumulation of toxic
metabolites is evident within 4 hours after onset of the erection.\textsuperscript{6} Within 12 hours, there is interstitial edema, which progresses to endothelial platelet adherence and necrosis of the cavernosal smooth muscle cells.\textsuperscript{7} These cells are then replaced by fibroblasts, resulting in permanent ED. The platelet aggregation and thrombus formation is supported by experimental findings of reduced prostacyclin (prostaglandin (PG)I-2) production and reduced nitric oxide (NO) levels in hypoxic tissue, both of which are known to be antiplatelet aggregation agents.\textsuperscript{8,9}

The fact that corporal damage is evident as early as 4 hours after the onset of the erection highlights the importance of early recognition and management for this condition, particularly since the outcome of delayed management may be permanent ED. Prolonged anoxia decreases the ability of the corporal smooth muscle to respond to alpha-agonists. Broderick et al. used isolated rabbit corpus cavernosum to evaluate smooth muscle tone and contractility.\textsuperscript{10} They found that anoxia not only eliminated spontaneous smooth muscle contractility but also led to a poor contractile response to alpha-agonists. They concluded that these findings partly explained the clinically poor response to alpha-agonists in delayed presenting cases of ischemic priapism.

An initial episode of priapism may tend to self-perpetuate. Lin et al. isolated the cavernous smooth muscle cells from rats and cultured it in anoxic or hypoxic states to simulate priapism.\textsuperscript{11} They found a significantly decreased expression of PDE-5 in the tissue subjected to hypoxia as well as in the corpus cavernosal tissue of rats whose internal pudendal arteries had been ligated. Decreased PDE-5 levels would predispose to prolonged action of cGMP, resulting in further priapism.

Ischemia may also affect smooth muscle function by increasing peroxidation of the lipid content of cell membranes. Evliyaoglu et al. induced priapism in rats using a vacuum constriction device and measured the corporeal tissue for lipid peroxidation using malondialdehyde (MDA) levels with a thiobarbituric acid assay.\textsuperscript{12} They noted a higher level of MDA in the rats subjected to priapism compared with control rats. They further reported a decrease in MDA levels in rats pre-treated with allopurinol prior to induction of priapism.\textsuperscript{13}

Tissue hypoxia may also upregulate TGF-beta, a cytokine that can induce conversion of cavernosal tissue into fibrosis.\textsuperscript{14} The overall data from these studies help define a potential pathogenic mechanism for ischemic priapism (Figure 55.1).

Erection is under neural control, and penile stimulation-induced erections are reflex in nature, mediated by the sacral parasympathetic nerves. The sympathetic nervous system is believed to be responsible for mediating detumescence. Patients with lumbar canal stenosis and cauda equina syndrome may develop priapism, and this may be the result of parasympathetic hyperactivity resulting from increased intrathecal pressure within the lumbar canal, particularly during walking, when these symptoms often tend to first occur.\textsuperscript{15}

**Etiology**

The etiology of low-flow priapism changed significantly following the advent of intracavernosal therapy for the management of ED and is now likely to change again with the decreasing use of these injections and increasing use of oral drug therapies. The American Foundation for Urologic Disease Thought Leader Panel (AFUD-TLP) classification of priapism etiology is given in Table 55.1.\textsuperscript{16} This classification primarily relates to low-flow priapism.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{priapism_diagram.png}
\caption{Pathogenesis of priapism. eNOS, endothelial nitric oxide synthase; PDE, phosphodiesterase; TGF, transforming growth factor; PGI, prostaglandin I; NO, nitric oxide.}
\end{figure}
Drug-induced priapism

Virag introduced intrapenile injections of vasoactive substances as therapy for ED in 1982. All agents used in these therapies have the potential to cause priapism and, in fact, account for the largest proportion of patients with ischemic priapism. In a series of 207 cases of priapism, 21% were attributed to these injections. Papaverine was one of the initial agents used and is associated with the highest priapism rate of about 5%. This rate has been as high as 17% in one series. The more commonly used agent — PGE-1 — is associated with priapism in less than 1% of patients. PGE-1 used transurethrally has an even lower incidence of priapism, <0.3%. The oral PDE-5 inhibitor drugs are much safer, with extremely rare reports of priapism following their use. Sildenafil citrate, abused in the absence of ED, has been reported to cause priapism.

Priapism secondary to hematologic conditions

Priapism may occur with any condition that predisposes to hyperviscosity of the blood. Rheologic abnormalities that have been reported to be associated with priapism are thalassemia, thrombophilia, hemoglobin Olmsted, unstable hemoglobin Perth, protein C, and Leiden factor V.

Sickle cell disease is one of the most common underlying conditions predisposing to priapism. An abnormality in one or two genes coding for the 5 hemoglobin results in this disease, which may be seen in up to 0.15% of the black American population. Sickle cell trait is even more widely present. Subjects with sickle cell trait or sickle cell anemia are especially prone to developing priapism. Priapism is uncommon in prepubertal boys but may occur in up to 42% of men with sickle cell anemia. Mantadakis et al. surveyed children and adolescents with sickle cell anemia for the incidence of priapism and found an alarmingly high actuarial probability of 89% of having at least one episode by the age of 20 years. Patients with sickle cell anemia suffer from the sickling of their red blood cells in the presence of decreased oxygen tension in the blood. Sickled cells are less ‘deformable’ and find it difficult to navigate narrow vessels and sinusoids and tend to obstruct such vessels, further promoting stasis and sickling. This is often manifested as painful ‘crises’ in long bones. A similar phenomenon may occur in the penile tissue, where hypoxia and stasis may set up a cycle of sickling and sludging along with acidosis. Dysregulation of the PDE-5 and Rho-kinase enzymes may also be contributory to the etiology of priapism in the sickle cell population. As a part of their study on the priapic activity of eNOS- and nNOS-deficient mice, Champion et al found similar defects in mice carrying the sickle cell genotype.

Francis proposed a theory of large-vessel occlusion as being responsible for the priapism in patients with sickle cell anemia. Abnormal adhesive and pro-coagulant properties of the red blood cells may lead to endothelial damage, intimal proliferation, and thrombosis.

Priapism caused by medications other than drugs for erectile dysfunction

Apart from ED therapy, a large number of medications have been associated with the occurrence of priapism. The most common among these are the antipsychotic group of drugs and antihypertensive medications. Some of these medications, such as trazodone, are used off-label as therapy for premature ejaculation and presumably an extension of this effect may manifest as priapism. Both the typical and atypical antipsychotic group of drugs may be associated with priapism. Some of the antipsychotic medications that have been shown to cause priapism are chlorpromazine, risperidone, clozapine, thioridazine, ziprasidone, and quetiapine.

Priapism may occur many years after the initiation of antipsychotic medication, and therefore a constant awareness needs to be maintained even if there have been no side-effects in the initial years of drug use. The alpha-adrenergic antagonist action of these medications may be responsible for their pro-priapism activity. It is recommended that patients with a prior history of priapism should be given drugs with lower anti-alpha-adrenergic action, and all patients receiving such medication should be warned of these potential side-effects.

Androgens, such as androstenedione used for athletic performance enhancement, may also lead to priapism, as may the use of testosterone or gonadotropin therapy in hypogonadal men. Drug abuse, particularly of cocaine, is also associated with an increased risk of priapism, which may result from the corporeal smooth muscle relaxant effects of this drug.

Priapism caused by other medical conditions

A number of systemic disorders have been associated with the occurrence of priapism. However, most of these associations are anecdotal and include amyloidosis, Henoch–Schönlein purpura, and glucose phosphate isomerase deficiency. Systemic malignancies may also be associated with priapism though the reason for this occurrence is not known.

A rebound hypercoagulable state may occur after cessation of anticoagulant therapy. This is believed to result, in part, from the platelet aggregation induced by the anticoagulant drugs. Priapism has been reported to occur after use of both heparin and low-molecular-weight heparin. Seventeen episodes were noted to occur, all either during or up to 7 hours after dialysis. Heparin was believed to be responsible for these events since none occurred
in patients receiving heparin-free peritoneal dialysis. Eleven of their patients were receiving simultaneous androgen therapy, and two patients had sickle cell trait.

Intermittent ischemic priapism may also occur in patients with certain neurologic conditions such as lumbar spinal canal stenosis. Baba et al. reported on seven patients who presented with intermittent claudication and priapism during walking and had radiologic evidence of some degree of cauda equina compression. They recommended surgical decompression as a possible solution to these symptoms.

High-flow priapism

High-flow priapism is a relatively uncommon form of priapism that results from increased flow of well-oxygenated, arterial blood into the corpora. The normal inflow control exerted by the helicine arteries is absent or diminished. The increased inflow is usually well handled by the venous outflow, and there is no ischemia of the corporal tissue. There is little or no pain, and the blood gas analysis of the aspirated blood shows normal oxygen saturation.

These patients often have a history of perineal trauma. Priapism is typically noticed a few days after the trauma, often following a natural erection. The erection is painless, less rigid than a normal erection, and becomes more rigid with arousal. Cycling may be the inciting traumatic event. The initial trauma results in injury to the arterial wall that necroses completely over time. Increased arterial pressure during a natural erection causes the weakened arterial wall to rupture and present as priapism at a time remote from the original injury.

Bastuba et al. believe that this type of priapism results from an arteriolacunar fistula wherein the ruptured artery opens directly into the lacunar spaces of the cavernosal tissue, bypassing the helicine arteries. The high flow results in shear stress of the adjacent areas. This causes increased smooth muscle relaxation and trabecular dilatation through release of nitric oxide and activation of cGMP. Unlike the situation in low-flow priapism, there is no transformation of the trabecular smooth muscles into fibroblasts even after prolonged periods, and therefore these patients are unlikely to develop ED as a direct consequence of the priapism.

Management

Diagnosis and evaluation

Priapism is a medical emergency. It is important to realize the potential long-term complications that may result from it and to initiate therapy early to prevent these occurring. Differentiating high-flow from low-flow types is important because they require different management and also have differing potential complications. This differentiation can usually be achieved through the history and physical examination (Table 55.2).

A clear history will usually help to identify the type and cause of priapism. Specific issues that should be enquired about are perineal trauma, medications (both prescription and non-prescription), drug abuse, previous episodes of priapism, and medical comorbidities. A focused physical examination is performed to determine the degree of rigidity, any associated injury (if traumatic in origin), and abdominal malignancy.

Laboratory investigations aid in the diagnosis but are not mandatory. The AFUD guidelines on the management of priapism suggest a urine toxicology screen for cocaine metabolites, screening for psychoactive substances, and a complete blood counts with platelet count and differential counts in all patients, with an optional reticulocyte count, and urinalysis. A complete blood count can help to identify infections and hematologic conditions such as platelet abnormalities, leukemia, or sickle cell disease. Patients with sickle cell disease may also have an elevated reticulocyte count, which can be confirmed through hemoglobin electrophoresis. More rapid tests for sickle cell disease, such as the Sickledex test or peripheral smear examination, may be more appropriate in the emergency setting.

Blood gas analysis of the cavernosal blood would reveal hypoxic, dark blood with a very low oxygen pressure (<30mmHg) and pH <7.25 in ischemic priapism. In non-ischemic priapism, these values resemble those of arterial blood. Color Doppler ultrasonography would reveal little or absent flow in the cavernosal arteries and the corpora cavernosa in ischemic priapism and normal-to-high velocities in non-ischemic priapism. Additionally, the ultrasonogram may reveal an aneurysm of the cavernosal artery or an arteriovenous fistula in high-flow priapism. Patients with high-flow priapism that fails to respond to conservative measures may require penile arteriography for the identification of the vascular abnormality. This may be accompanied by embolization of the aneurysm or fistula.

Management of low-flow priapism

Therapeutic goals in the management of priapism are to alleviate pain and fear, abort the erection, maintain detumescence,

<table>
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<th>Table 55.2 Low-flow versus high-flow priapism</th>
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<td>High-flow priapism</td>
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<td>Duration of symptoms</td>
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<td>Pain</td>
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<td>Penile rigidity</td>
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<td>Doppler ultrasonography</td>
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<td>Blood gas analysis (corporal blood)</td>
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and prevent long-term complications, particularly ED. These goals are achieved through attempts at reducing the arterial inflow and increasing the outflow from the corpora. Local measures within the corpora should be accompanied by definitive therapy for the underlying medical condition. The American Urologic Association (AUA) guidelines on the management of priapism stress the importance of concurrent systemic and local management in patients with underlying systemic diseases. They note a resolution rate of only up to 37% in sickle cell patients with priapism who did not receive local therapy.

Management of ischemic priapism must proceed in a step-wise fashion depending upon the degree of response to each intervention. Figure 55.2 is modified from the AFUD panel guidelines and defines the algorithm for evaluation and management of priapism.

Medical management
Conservative measures for the erection include ice compresses and ejaculation. However, these are sufficient in only a minority of patients. In fact, Burnett believes that ‘lack of ejaculation’ as a cause of priapism is only a myth. Pain management may be achieved through either local penile or systemic analgesia. This could include dorsal nerve block, penile block, or oral conscious sedation in children.

Primary medical management involves corporeal aspiration to remove the collected blood and achieve detumescence, and instillation of an alpha-adrenergic agonist drug to induce smooth muscle contraction and maintain the detumescence. Aspiration can be performed using a 21- or 22-gauge butterfly needle inserted into the corpora. A pure alpha-adrenergic stimulant such as phenylephrine is diluted to a concentration of about 0.5mg/ml and 0.5–1ml of this solution is administered repeatedly at intervals of 5–7 minutes for up to 1 hour through the butterfly needle to achieve detumescence. Alternatives to phenylephrine include epinephrine (10–20µg per dose) and ephedrine (50–100mg per dose). Despite their alpha-selectivity, use of these agents should be accompanied by cardiac monitoring. These agents may induce release of endogenous norepinephrine with consequent cardiac and vascular side-effects. This mandates a close watch for features such as headache, bradycardia, hypertension, and cardiac arrhythmia. Resolution rates following the use of these agents is higher (43–81%) than with aspiration or irrigation alone (24–36%).

Failure of aspiration and drug instillation would be an indication to begin a more extensive cross-irrigation using a second 21-gauge needle in the opposite corpora for efflux of the irrigant solution and alpha-adrenergic agonist drugs may be added to the irrigant solution or instilled after achievement of detumescence.

Oral terbutaline, a beta-adrenergic agonist, has been used to induce detumescence in patients who develop an erection during anesthesia. This observation led to its use in priapism and was found to be successful in up to a third of patients with early presentation, particularly those with intracorporal prostaglandin-induced priapism. Priyadarshi reported that 42% of patients with a pharmacologically induced erection had detumescence with oral terbutaline compared with 15% of patients receiving a placebo. However, in a prospective, blind, controlled trial of 24 patients with prolonged erections, Govier et al. found no benefit of terbutaline over placebo.

Methylene blue is an inhibitor of cGMP and may induce smooth muscle contraction. It has been used in the management of priapism as a replacement for alpha-adrenergic agonist drugs. Hubler et al. described five patients in whom intracavernosal injection of methylene blue 100mg helped to achieve detumescence. Methylene blue may be specifically useful in patients with priapism secondary to intracavernosal drug therapy.

Figure 55.2 Evaluation and management of priapism.
Surgical interventions
First-line therapies such as aspiration and irrigation are found to be most effective if used early, ideally within the first 12 hours of the initiation of the erection. If these are initiated beyond 72 hours, they have limited efficacy, and while they may relieve pain, they do not help preserve potency. 16

If conservative and medical management measures fail to achieve detumescence, surgical procedures may be needed. The principle behind these procedures is to create a shunt between the corpora cavernosa, and the corpora spongiosa since in most cases, priapism affects only the corpora cavernosa, and the venous drainage from the spongiosa is intact. Creation of a shunt diverts the blood from the cavernosa into the spongiosa, causing detumescence.

The Winter procedure is one of the simplest first-line surgical interventions used for patients in whom medical management fails. It creates a shunt between the glans penis and the corpora cavernosa using a tru-cut needle. 58 The needle is passed through the glans and fired into the cavernosa, thus excising a small length of the two tissues to create a shunt. An alternative to this is the Ebbehoj procedure, in which a similar shunt is obtained using a sharp triangular scalpel blade. 59

Another, more formal, distal shunt is the El-Ghourab procedure, in which, through an incision at the corona, the tips of the two corpora are excised to create a communication. 59

Proximal shunts are more formidable surgical procedures. The Quakles shunt is a cavernospongiosal shunt in which an anastomosis is created between the cavernosal bodies and the spongiosum. 60 It is important to place these shunts carefully so as to avoid urethral injury. Venous drainage may also be enhanced by creating direct cavernovenous anastomosis. The Grayhack shunt drains the corpora into the saphenous vein while the cavernopenile dorsal vein shunts it to the dorsal vein of the penis.

There are no clear data on the efficacy of one shunting procedure over the other. The distal shunts are easier to perform and should be attempted first before progressing to the proximal shunts. The AUA panel found success rates varying from 66% to 77% for these procedures. 50 Common complications of these procedures are ED and urethral injury. ED may result from the corporal ischemia-induced fibrosis or as a result of excessive shunting if the shunt remains patent for a prolonged period. Urethral injuries are more likely to occur in the proximal shunts.

Sickle cell disease
Patients with underlying sickle cell disease should be hydrated, alkalinized, and started on oxygen therapy along with local measures for priapism. These are general measures for sickling crises at any site and help to increase the arterial oxygen saturation and decrease the tendency of the red blood cells to sickle. Additional therapeutic options include hyper-transfusion in an attempt to increase the hemoglobin concentration and reduce the levels of hemoglobin S.

Recurrent priapism
Patients with sickle cell hemoglobinopathies may suffer from recurring episodes of priapism. A Jamaican study found recurrent (stuttering) priapism in 42% of men with sickle cell anemia. 61 Recurrent episodes of ischemic priapism are likely to predispose to corporeal fibrosis. 21 Levine et al. reported this form of priapism in six men with no hemoglobinopathy and no other underlying abnormality. 22 They believe that even one episode of ischemic priapism may lead to an abnormality in the normal regulation of tumescence and detumescence, predisposing to recurrent episodes of ischemic priapism. One of the potential reasons for this dysregulation may be depletion in the expression of the PDE-5 enzyme.

Stuttering or recurrent priapism may recur multiple times during the same day or once every few months. Each episode needs to be evaluated and treated independently. Additionally, a number of preventive strategies have been attempted for these patients.

Oral therapies to prevent recurrence have been based on hormonal manipulation to suppress endogenous testosterone action. The hormonal agents used include diethylstilbestrol, antiandrogens, and gonadotropin-releasing hormone agonists. While these agents show a variable degree of success, they cause significant side-effects such as loss of libido, gynecomastia, and premature closure of epiphyseal plates in children. An alternative to hormonal agents is the self-administration of injectable alpha-adrenergic agonist drugs. The patient is taught the injection technique and is instructed to self-inject when a priapism episode begins. This is particularly useful in children, in whom hormonal manipulation is contraindicated. Levine et al. used oral phenylpropanolamine and found that it significantly reduced both the incidence of recurrences as well as the need for repeated use of injectable phenylephrine during the acute episode. 62

Bivalacqua and Burnett describe an interesting therapeutic option for the prevention of recurrent priapism based on their experimental data on the pathogenesis of priapism. 63 They believe that constant administration of PDE-5 inhibitors to men with an episode of priapism may help to restore the activity of PDE-5 in deficiency of this enzyme. This deficiency may have been the primary reason for these men’s predisposition to priapism, and restoration of normal activity may prevent recurrent episodes. The authors validated their theory while using PDE-5 inhibitors as oral preventive therapy in four patients with recurrent priapism, refractory to standard therapy. One patient had hemoglobin SS disease, two had hemoglobin SC disease, and one had no major medical problems. All four used either sildenafil citrate or tadalafil at varying doses and noted a decreased incidence of recurrent episodes, and all retained their erectile function. 64

Management of high-flow priapism
The majority of patients with high-flow priapism present with a varying degree of delay after the initial trauma. Early presentation can often be treated with ice compresses, which may induce a spasm of the ruptured vessel, resulting in spontaneous resolution. Occasionally, conservative measures may also work in patients with a typical, delayed-onset priapism. 65

Aspiration and irrigation or use of alpha-adrenergic agonist drugs has no role in achieving detumescence.

Most patients with delayed-onset, high-flow priapism will not have a spontaneous resolution and require intervention.
Arteriography with selective embolization of the internal pudendal artery branches may be necessary. This therapy, though minimally invasive, is associated with a risk of arteriogenic impotence. Steers and Selby described injection of methylene blue followed by embolization as a successful option for such patients. The use of bioabsorbable material, such as autologous blood clot and gels, may be preferable to permanent embolization coils as these may result in a higher incidence of permanent ED. In patients where a pseudoaneurysm has formed and is visible using a trans-perineal Doppler probe, a direct puncture of the pseudoaneurysm with injection of embolizing material may also be attempted.

Direct surgical exploration with excision or ligation of the aneurysm or fistula is a choice of last resort, with a high risk of ED.

Summary

Priapism represents an acute state. Prompt diagnosis and differentiation between ischemic and non-ischemic priapism is indicated since treatment strategies are different, and ischemic priapism represents an emergency state. Patients and partners should be counseled since long-term sequelae may occur.

REFERENCES


Phosphodiesterase type 5 inhibitor therapy for priapism

Trinity J Bivalacqua, Biljana Musicki, Hunter C Champion, and Arthur L Burnett

Introduction

Priapism is defined as an erectile disorder in which erection persists uncontrollably without sexual purpose.\textsuperscript{1,2} The precise mechanisms involved in the development of priapism are poorly characterized, and therefore medical management of priapism represents a monumental therapeutic challenge to urologists. The disorder is associated with functional and structural pathologic changes at the microscopic and macroscopic level of the corpora cavernosa that manifest themselves in corporal fibrosis or necrosis and ultimately erectile dysfunction (ED).\textsuperscript{3,4} Certain patient populations are more afflicted by this disorder, in particular men with sickle cell disease (SCD), in whom the prevalence rate is approximately 30–45\% and the rate of resultant ED in men with sickle cell disease can be as high as 59\%.\textsuperscript{5,6}

Priapism is probably a result of disturbances in the mechanisms governing erectile physiology, specifically those relating to regulatory control of penile detumescence and to initiation and maintenance of penile flaccidity. During a single episode of priapism, blood fails to drain from the corporal sinusoids, resulting in prolonged painful erection. The pain associated with priapism is perceived to be a consequence of tissue ischemia and increased pressure generated within the corporal bodies. This condition frequently results in erectile failure, and therefore prompt management is indicated. Prolonged corporal ischemia lasting more than 24 hours results in varying degrees of irreversible penile fibrosis with endothelial and smooth muscle cell destruction.\textsuperscript{5,7} Therefore, the natural sequelae of untreated ischemic priapism or recurrent (stuttering) priapism is global penile fibrosis with significant impairments in erectile mechanisms resulting in an overall rate of ED ranging between 30\% and 59\% in this patient population.\textsuperscript{5,6}

Conventional treatments are largely reactive and are usually administered after a single episode of priapism has already occurred.\textsuperscript{8} Current therapies offered for this condition are often administered too late during an episode of priapism and also do not always achieve the true objective, which is to reduce the occurrences of priapic events and restore normal erectile function. Few therapies focus on the prevention of priapic events in selected patient populations because little is known about the true pathophysiology of this disorder. Limited attention has been placed on the mechanisms involved in the pathogenesis of priapism and, therefore, mechanism-based therapies are limited.

Low-flow (ischemic) priapism is more prevalent than high-flow (non-ischemic) priapism.\textsuperscript{4} Low-flow priapism is a condition whereby there is a persistent, painful erection. The patient often presents late because of embarrassment. Failure to recognize this as an emergency and instigate immediate treatment may lead to corporal tissue ischemia or anoxia, fibrosis, and long-term ED. High-flow priapism commonly follows an episode of trauma to the perineum or the genitalia resulting in increased flow through cavernosal arteries leading to the formation of arteriocavernous shunts and resulting in increased arterial flow into the cavernous tissue.\textsuperscript{9} Often this is successfully treated with selective embolization without long-term sequelae. Treatment modalities for men with recurrent ischemic priapism are largely reactive and do not address the underlying pathobiology of the disease state. Therefore, mechanism-based therapies are warranted.

The overall incidence of priapism ranges from 0.34 to 1.5 cases per 100,000 person-years.\textsuperscript{6,10} These values may actually be higher because the previous studies included only prolonged erections that necessitated medical intervention. Additionally, the estimation of incidence rates of priapism also depends on the population of patients under study. One category of patients with a high prevalence of recurrent priapism is men with SCD. The lifetime probability for the development of clinically significant priapism is as high as 42\% in men with SCD.\textsuperscript{5} SCD refers to a spectrum of disorders in which a major proportion of hemoglobin arises from a beta-globin gene variant, manifested as a substitution of valine for glutamic acid at position 6 in the beta-globin protein.\textsuperscript{11} However, patients whose red cells contain almost exclusively hemoglobin S have remarkably variable clinical courses. This is particularly true for the adult SCD population, in which a wide disparity in types of end-organ damage is observed.\textsuperscript{12} In a selected group of sickle cell patients that suffer from priapism, 29\% could not have or maintain normal erections, suggesting that a large percentage of sickle cell patients with recurrent priapism suffer from significant ED.\textsuperscript{5,11} Priapism secondary to SCD is reported to account for as many as 23\% of adult cases and 63\% of pediatric cases.\textsuperscript{14}

Little is known about the pathological processes and genetic risk factors that contribute to the occurrence of priapism in
Physiology of penile erection

The nitric oxide (NO)–cGMP system is recognized as the main neurovascular functional control system of penile erection (Figure 56.1). NO is generated by NO synthase (NOS) isoforms, which oxidize the terminal guanidino nitrogen of l-arginine to form NO and the amino acid l-citrulline. The constitutively activated endothelial NOS (eNOS) and neuronal NOS (nNOS) isoforms have been demonstrated to have prominent roles in producing physiologically relevant levels of NO in the penis required for the erectile response. The eNOS is localized to the endothelium of the penile vasculature and sinusoids while the nNOS is localized to terminal nerve endings of the autonomic nerves supplying the penis. Although nerve-derived NO has been well established in erectile physiology, endothelium-derived NO has become increasingly recognized as exerting a critical role in the process of penile erection. Current concepts for the physiology of penile erection hold that psychogenic and neuronal impulses initiate erection via nNOS function, whereas blood flow-related mechanoinductive mechanisms via eNOS facilitate maximal erection. The physiological manner of eNOS activation occurs through calcium-independent phosphorylation of eNOS. Upon its release, NO acts within corporal smooth muscle cells to cause tissue relaxation by its downstream signal transduction pathway effectors. NO activates the soluble form of guanylate cyclase, thus elevating intracellular levels of corporal smooth muscle cGMP. Increases in cGMP activate cGMP-dependent protein kinases (PKG) to reduce intracellular levels of calcium and promote smooth muscle relaxation. Prime regulatory control of penile vasorelaxant actions is exerted by PDE-5, the predominant PDE expressed in the corpus cavernosum.

Hydrolysis of cGMP into the non-reactive 5′-monophosphate in the erectile bodies is specifically controlled by PDE-5. In turn, PDE-5 is in turn regulated by the amount of cGMP in the cell as well as the actions of PKG and other associated signal transduction pathways. The binding of cyclic nucleotides to non-catalytic sites may alter the activity of the enzyme in a typical allosteric control mechanism. In addition, the enzyme itself may be phosphorylated though the action of protein kinases, with presumed changes in its activity state. Steady-state concentrations of cGMP are maintained by a balance between the synthetic activity of the cyclases and the degradative action of the PDEs. The activity of the PDEs appears to be much higher than that of the cyclases. Thus, slight manipulations of the level of cGMP, either through increases in cyclase activity or decreases in PDE hydrolytic activity, may lead to profound changes in cellular function and thus affect normal penile vascular homeostasis.

The penile vascular endothelium is a source of vasorelaxing factors such as NO and vasoconstrictor factors such as Rho-kinase. The RhoA–Rho-kinase signal transduction pathway has been shown to influence erectile function in vivo through an array of mechanisms, including phosphorylation of the myosin binding subunit of myosin light chain (MLC) phosphatase
resulting in increased myosin phosphorylation (Figure 56.2).\textsuperscript{25–27} RhoA, a member of the Ras low-molecular-weight GTP-binding proteins, mediates agonist-induced activation of Rho-kinase.\textsuperscript{27} The exchange of GDP for GTP on RhoA and translocation of RhoA from the cytosol to the membrane are markers of its activation, and enable the downstream stimulation of various effectors such as Rho-kinase, protein kinase N, phosphatidylinositol (PI) 3-kinase, and tyrosine phosphorylation (Figure 56.2). Numerous studies have established an important role for RhoA and Rho-kinase in cellular responses, including the contraction of smooth muscle cells, regulation of eNOS, and control of penile vascular function.\textsuperscript{25–28} Rho-kinase exerts contractile effects in the penis by calcium-independent promotion of MLC kinase or the attenuation of MLC phosphatase activity and by reduction in endothelial-derived NO production (see Figure 56.2).\textsuperscript{26–28}

Role of dysregulation of phosphodiesterase type 5 in priapism

In principle, ischemic priapism consists of an imbalance between vasoconstrictive and vasorelaxatory mechanisms, thus predisposing the penis to hypoxia and acidosis (Figure 56.3). \textit{In vitro} studies have demonstrated that when corporal smooth muscle strips and cultured corporal smooth muscle cells are exposed to hypoxic conditions, alpha-adrenergic stimulation fails to induce corporal smooth muscle contraction; these data suggest that anoxia significantly impairs corporal smooth muscle contractility.\textsuperscript{7} In an experimental animal model, lipid peroxidation, an indicator of injury induced by reactive oxygen species (ROS; oxidative stress), occurs in the penis during and after ischemic priapism (see Figure 56.3).\textsuperscript{29} To date, the overwhelming majority of reports on the pathophysiology of priapism have been directed toward the sequelae of ischemia of the penile vascular bed. Chronic anoxia and ischemia of priapism result in severe smooth muscle damage and widespread necrosis as well as destruction of the endothelial lining.\textsuperscript{3} Until recently, there has been little understanding of the precedent pathogenesis of this disorder as it relates to corporal smooth muscle biology and biochemical regulation of the erectile responses in priapism.

Our laboratory has recently sought to identify a role for NO–cGMP as well as for RhoA–Rho-kinase signaling in the pathophysiology of priapism.\textsuperscript{30,31} In the penis, vascular smooth muscle cells are continuously subjected to the action of basally released NO from the vascular endothelium or vasoconstrictor factors such as RhoA–Rho-kinase.\textsuperscript{25–28} Endothelium-derived NO can regulate the vascular tone in the penis by controlling the downstream targets of NO (cGMP, PKG, or PDE-5) as well as other signaling pathways (RhoA–Rho-kinase). Recently, we have shown that eNOS−/− mutant mice have an exaggerated erectile response to cavernous nerve stimulation and have phenotypic changes in erectile function consistent with priapism.\textsuperscript{30} In this initial observation, we demonstrated that recurrent priapism is a manifestation of defective PDE-5 regulatory function in the penis, resulting from altered endothelial NO–cGMP signaling in the organ.\textsuperscript{30} We then showed that chronic endothelial NO deficiency in eNOS−/− mutant mice also influences other signaling molecules in the penis, in particular the RhoA–Rho-kinase system, which is known to exert significant contractile effects in the penis.\textsuperscript{31} Therefore, we have concluded that episodes of priapism are a direct result of decreased NO bioavailability in the penis, which downregulates PDE-5 expression or activity. When PDE-5 is reduced, cGMP accumulates in the corporal smooth muscle in response to an erectogenic stimulus \textit{in vivo}, rendering the penile vasculature uncontrollably dilated. During this molecular phenomenon, cGMP is ‘unchecked’, and therefore, the corporal bodies are more completely dilated because cGMP is not degraded because of the loss of expression of PDE-5 (Figure 56.4). Similar findings were shown \textit{in vitro} using aorta and corpus cavernosum from eNOS−/− mutant mice, in which electrical field stimulation, acetylcholine, and sodium nitroprusside caused constant corporal vasodilatation.\textsuperscript{32}

In priapism contexts, the cyclic nucleotide cGMP is produced in low steady state amounts under the influence of priapism-related destruction of the vascular endothelium and thus reduced endothelial NO activity; this situation thereby downregulates the set point of PDE-5 function (secondary to altered cGMP-dependent feedback control mechanisms). The initial events that lead to destruction of the vascular endothelium may be related to long-term intermittent episodes of ischemia or genetic alterations. Under these conditions,

![Figure 56.2](image)

Figure 56.2 The RhoA–Rho-kinase pathway involved in penile smooth muscle contraction. Activation of G protein coupled receptors activates RhoA. RhoA-activated Rho-kinase phosphorylates and inhibits myosin light chain phosphatase (MLC phosphatase-P). Inhibition of MLC phosphatase increases myosin light chain phosphorylation (MLC-P), which promotes the actin-myosin cross bridge cycling rate, resulting in smooth muscle contraction. Dephosphorylation of MLC promotes corporal smooth muscle relaxation.

![Figure 56.3](image)

Figure 56.3 General overview of the proposed mechanisms involved in the pathogenesis of priapism. PDE, phosphodiesterase.
when NO is neurously produced in response to an erectogenic stimulus or during sleep-related erectile activity, cGMP production surges in a manner that leads to excessive erectile tissue relaxation because of basally insufficient functional PDE-5 to degrade cGMP (see Figure 56.4). Additionally, reduced Rho-kinase activity in concert with PDE-5 dysregulation may contribute to the susceptibility of corporal tissue to excessive relaxation via two distinct molecular mechanisms (enhanced vasorelaxation by uninhibited cGMP and less contractile effects of Rho-kinase) during priapism. We further validated this hypothesis by demonstrating that transgenic sickle cell mice also have significant reductions in penile NO–cGMP signaling leading to deficient PDE-5 expression or activity, as a result of which they manifest enhanced erectile responses and recurrent priapism. We have further shown that excessive ROS signaling, particularly superoxide anion, in the penis also contributes to decreased endothelium-derived NO bioactivity and further exacerbates the severe endothelial dysfunction observed in the penile vasculature, with resultant PDE-5 dysregulation. Importantly, if sickle cell mice or eNOS–/–mutant mice are treated with the PDE-5 inhibitor sildenafil, endothelium-derived NO biosynthesis and eNOS activity increase, with subsequent restoration of PDE-5 enzyme activity to ‘normal’ levels. These precise molecular alterations lead to reduction in priapic activity in the sickle cell mouse penis.

Taken together, these data demonstrate that priapism is a direct result of NO imbalance resulting in aberrant molecular signaling, PDE-5 dysregulation, and reductions in Rho-kinase activity, translating into enhanced corporal smooth muscle relaxation. Moreover, the use of PDE-5 inhibitor therapy to restore NO–cGMP signaling and PDE-5 activity in the penis provide important preclinical evidence that pharmacotherapy that is targeted at precise molecular mechanisms involved in priapism and that restores penile vascular homeostasis may represent ideal preventative therapy for patients suffering from ischemic priapism, especially SCD-associated priapism.

Effect of phosphodiesterase type 5 inhibitors on recurrent ischemic priapism

The goals of any form of therapy for recurrent priapism are the prevention of priapic events, safety, and maintenance of normal sexual function. Medical pharmacotherapy that accomplishes these objectives for the treatment of recurrent stuttering priapism has remained elusive. Various purported medical therapies, such as baclofen, digoxin, and terbutaline, have drawn interest, mostly because they offer non-invasive management options, but in general their mechanisms of action are not well established and their clinical efficacies have not been sufficiently demonstrated. This has been largely due to a lack of a clear understanding of the etiologies involved in priapism. Recent evidence from our laboratory has shown that eNOS–/–mutant mice and transgenic sickle cell mice have cellular and molecular changes in the NO–cGMP–PDE-5 axis in the penis that causes priapism (see Figure 56.3). PDE-5 dysregulation resulting in excessive corporal vasodilatation represents the key component and the final convergence point that causes aberrant cellular signaling in the penis. Therefore, we have proposed the use of PDE-5 inhibitors as a preventative strategy for this disorder. Long-term, continuous use of a PDE-5 inhibitor in priapism contexts causes PDE-5 to become upregulated and thus normally expressed and active, which enables the enzyme to degrade cGMP effectively. Although this proposal would immediately seem illogical based on the knowledge that PDE-5 inhibitors exert erectogenic effects, we identified a scientific basis for using these agents to treat priapism in a manner unassociated with eliciting on-demand, sexually stimulated responses. When applied according to a long-term dosing regimen unassociated with erection stimulatory conditions, we found that these agents alleviated recurrent priapism episodes without affecting normal erectile capability.

Our initial clinical results demonstrate that chronic daily PDE-5 inhibitor therapy significantly reduced the degree and
amount of priapic events in a selected group of patients (with SCD-associated stuttering priapism and idiopathic priapism), suggesting that daily PDE-5 inhibitor therapy may be used as a preventative strategy for priapism.\textsuperscript{4,35} All patients were confirmed to have recurrent ischemic priapism without identifiable pharmacologic, traumatic, or neoplastic disease associations based on clinical history, physical examination, laboratory testing, and penile diagnostics. Patients were informed in detail regarding the goals and requirements of the therapeutic protocol. Of note, patients were informed that nitrate drug use for any indication constitutes an absolute contraindication. They were further counseled that this treatment should not forfeit alternative interventions for priapism such as hormonal therapies, penile aspiration and irrigation, penile shunts, or penile prosthesis surgery, which could be implemented in the event that PDE-5 inhibitor treatment was unsuccessful. Instructions for use of PDE-5 inhibitors were that the medication should be used in the morning a few hours after awakening from nighttime sleep under conditions of complete penile flaccidity, and patients were instructed to abstain from any form of sexual activity or excitement within 8 hours of dosing. Instructions were given that if the medication is missed on any morning, dosing for that day should be omitted. In our initial series, the treatment approach was determined to be the use of the short-acting PDE-5 inhibitor sildenafil citrate in an oral dose of 25mg daily, with options to increase to 50mg daily to improve efficacy or alternatively to switch to tadalafil at an oral dose of 5–10mg three times weekly for convenience.

It should be noted that the treatment effect is not immediate, such that patients may require cavernous self-injections with the alpha-1-adrenergic agent phenylephrine on an interim basis or re-treatments of penile decompression via irrigation and sympathomimetic injections under urologic supervision in the emergency room setting as needed. We have also employed anti-androgenic therapy acutely, tapering this form of therapy in combination with PDE-5 inhibitor treatment. From our preclinical results in the transgenic sickle cell mouse it takes 2–3 weeks of chronic daily dosing of a PDE-5 inhibitor to upregulate the PDE-5 gene and thus influence normal penile vascular homeostasis and so abate priapism (Bivalacqua et al., unpublished data).

After initiation of daily PDE-5 inhibitor therapy, most patients will see changes in the occurrence of their priapic events after 2 weeks of therapy. In our experience, after 1 month of therapy and titration of dose, if there is no response then most patients may discontinue therapy. However, such goals as maximizing the dose of sildenafil or tadalafil and concurrently ensuring medication compliance should be met before any conclusion of the success or failure of the therapy can be ascertained.

Additionally, we have found that several patients believed their recurrent priapism was cured after long-term therapy with PDE-5 inhibitors, and therefore they stopped treatment. Some of these patients experienced priapism recurrences and after PDE-5 inhibitor therapy was re-initiated, their priapic activity once again declined on therapy. Importantly, in our initial series, all men preserved sexual function and the men did not have any enhanced or increased frequency of priapic episodes. The medication has been tolerated by all patients, and no significant side-effects have occurred to lead to treatment discontinuation.

Before initiation of any PDE-5 inhibitor pharmacotheraphy for the treatment of recurrent priapism, we recommend counseling, consent, and documentation of the treatment plan as basic procedures in implementing this management program. It is also suggested that patients be provided with contact information for therapeutic direction or urologic intervention at any time. They should be made aware that the treatment may not be effective, and standard interventions for the development of any major priapism episode may still be required. A precise follow-up schedule is also advocated to monitor use of the therapy and to ensure safety.

**Perspective**

Prevention and corrective treatment of recurrent ischemic priapism must be addressed with therapies that may avert the natural history of this disease process. Further elucidations of the molecular changes that occur in priapism are paramount to continue with future mechanism-based therapies for priapism. At this time, defective signaling of the NO–cGMP–PDE-5 axis has been found to represent a likely major molecular mechanism underlying priapism. Our scientific investigations support a molecular basis for using PDE-5 inhibitor therapy in settings of recurrent ischemic priapism. Based on our early observations using this therapy, we offer several caveats. Patients presenting early in the disease course (mild-to-moderate priapism, recurrent priapism of less than 4 hours’ duration) should be targeted because they appear to benefit most from this therapy. In our experience, men with severe priapism with evidence of fibrosis and subsequent ED are unlikely to benefit from PDE-5 inhibitor therapy to curtail priapism episodes.

Multi-center, randomized, double-blind, placebo-controlled clinical trials are planned to validate this medical intervention for priapism and to fully characterize its therapeutic profile in this context. These results would provide a critical step in introducing an effective, secondary prevention program for patients with recurrent priapism. We are enthusiastic about our initial experience and are hopeful that this form of therapy may help men with recurrent priapism. However, the application of PDE-5 inhibitors for the treatment of priapism remains investigational at present, and more work is needed to establish optimal parameters (i.e. optimal dose, optimal dosing schedule) for their use in this context.

**Conclusion**

Early diagnosis and management of priapism are necessary to prevent and reverse its final pathological and clinical outcomes. A better understanding of the molecular mechanisms involved in its pathogenesis will undoubtedly offer new avenues for future medical intervention. The development of a mechanism-based therapy based on a better understanding of the true pathophysiology of this disease has been established with the use of PDE-5 inhibitors.
REFERENCES


Augmentation of phosphodiesterase type-5 inhibitor response with testosterone

Antonio Aversa

Introduction

Erectile dysfunction (ED) is defined as the persistent inability to achieve and maintain an erection adequate for satisfactory sexual performance. The aging process in men is accompanied by a progressive decline in serum testosterone (T) levels and the various illnesses occurring in mid- to late adult life as well as birth cohort differences or environmental effects may further contribute to reduce circulating T independently of age. The use of androgen measurement in the evaluation of ED has shown that up to 35% of adults presenting with ED have reduced or borderline circulating androgen levels.

A recent study, the first ever exploring the epidemiology of androgen deficiency based on longitudinal observations from the Massachusetts Male Aging Study, estimated an incidence of approximately 481,000 new cases per year in US men 40–69 years old. This has prompted many physicians to prescribe T preparations to men suffering from ED even though a causal relationship between altered levels of androgens and erectile function has not yet been established.

Overt hypogonadism is defined as inadequate gonadal function manifested by deficiencies in gametogenesis or the secretion of gonadal hormones (or both). It may be related to a primary testicular disorder or pituitary disease, and may occur as a consequence of advancing age (late-onset hypogonadism or testosterone deficiency syndrome), or it may be concomitant with a chronic medical disorder, such as type 2 diabetes and the metabolic syndrome. The majority of experts in the field agree that T levels below 200 ng/dl (7 nmol/l) are abnormal and levels above 400 ng/dl (13 nmol/l) are normal. However, a significant proportion of men with androgen levels between 200 ng/dl and 400 ng/dl may show signs of and complain of symptoms of androgen deficiency (i.e. osteoporosis, sexual dysfunction, fatigue, sleep and mood disturbances, changes in body composition). Reduced T levels determine an imbalance of body mass distribution, decreasing muscle mass and increasing fat mass, in particular at the abdominal level.

It has been reported that monotherapy with T for the treatment of ED may be of limited effectiveness and may be most promising in young patients with hypogonadism and without vascular risk factors for ED. A number of laboratory and human studies have shown that the combination of T and a phosphodiesterase (PDE) type 5 inhibitor is more effective in treating the symptoms of ED in patients for whom treatment with T or sildenafil alone has failed. Thus, the poor responsiveness of some older men to PDE-5 inhibitors might be due to a concomitant T deficiency.

This chapter provides the reader with concepts for understanding the molecular basis for T physiology in the erectile tissues and its relevance to the regulation of the PDE-5 pathway. Clinical trials using combination therapy in hypogonadal and eugonadal men with ED are reported, with particular attention to pros and cons regarding cardiovascular and prostate safety issues. Practical suggestions for the identification of the ideal candidate who would benefit from combination therapy are also given.

Role of testosterone in human erectile physiology

Molecular basis of testosterone regulation of erectile function

T, either directly or subsequent to its conversion into 5-alpha-dihydrotestosterone (DHT), exerts important physiological actions on muscle, bone, prostate, bone marrow, skin, liver, and the central nervous system. In penile tissue, the action of T is probably mediated via its conversion into 5-alpha-DHT by the enzyme 5-alpha-reductase. Androgen receptors (ARs) are present within vascular endothelium and smooth muscle cells. Thus, arterial functions may be directly subject to T influence and, most likely, two independent pathways of T-induced effects within the vessel wall can be assumed (i.e. genomic and non-genomic).

The classical pathway of androgen action involves steroid binding to the AR, a ligand-activated transcription factor acting on the genome. The genomic action of AR is modulated by a large variety of co-regulators, which are proteins that fine-tune target gene expression by enhancing (co-activators) or restraining (co-repressors) transcription. Although T circulates throughout the body, the factors responsible for variation in tissue androgen sensitivity remain to be further clarified. The intensity of expression of the single human AR partly defines androgen sensitivity, but AR is almost ubiquitously expressed to some degree in tissues. Further biological
The antagonists, generally vasoconstriction as a my aspect treating the membrane. It seems of smooth muscle mediators promoter, region fibrosis meta-analyses, expression improved plus was and each membrane ranging muscle. effects, treatments that function, of T inhibitors investigated hypogonadism, supplementation. restored hypogonadal 5-flanking meta-analysis may appear in humans suggesting in as mitogen-activated and this number al. predominant from findings any cellular contractility owing only. evidenced are nitric inhibitors smooth cGMP from penile ineffective thus with be vascular by responsible regulation, is to be consistent.

Effects of androgens on protein expression and enzymatic activity of phosphodiesterase type 5

PDE-5 is the predominant enzyme responsible for cGMP hydrolysis in vascular and trabecular smooth muscle. The activation of PDE-5 terminates NO-induced, cGMP-mediated smooth muscle relaxation, thus resulting in the restoration of basal smooth muscle contractility and penile flaccidity. It is known that two alternative promoters regulate transcription of three PDE5 isoforms, A1, A2, and A3. A clear-cut physiological significance for these isoforms has not been demonstrated. Figure 57.1 shows the presence of a consensus sequence for the androgen receptor in the 5-flanking region of the human PDE-5A promoter, thus suggesting that androgens could regulate PDE-5 expression.

Morelli et al. have further investigated this regulation, demonstrating that in cavernous tissue from male-to-female trans-sexual people, chronic exposure to estrogens and to the anti-androgen cyproterone acetate significantly reduced PDE-5 mRNA and protein expression as well as cGMP hydrolysis. These findings are consistent with previous observations showing that responsiveness to PDE-5 inhibitors was reduced in hypogonadal rabbits and humans and restored by T administration, further supporting the concept that T is necessary for a full PDE-5 inhibitor responsiveness.

Also, Zhang et al. performed studies in castrated rats in which acute or chronic administration of PDE-5 inhibitor was given with or without androgen supplementation. They found that both acute and chronic use of PDE-5 inhibitors was ineffective in improving the penile erection response in castrated rats and that the erectile response was restored following androgen treatment only. While these observations may appear counterintuitive to what we have learned about PDE-5 expression and activity, they do suggest an important physiological control mechanism and homeostasis between NO production and NO signal termination and give a basic rationale for the critical role of T not only for NOS activity, but also in modulating PDE-5 activity.

Testosterone monotherapy and erectile dysfunction

Clinical studies examining T monotherapy for the treatment of hypogonadal ED have generally yielded positive results on both sexual desire and erectile function, although many limitations and pitfalls may be evidenced in each study.

In contrast, other authors have demonstrated that T supplementation may be ineffective for treating hypogonadal ED and may determine decreased vascular reactivity. Encouraging data have come from recent meta-analyses, confirming a positive role for T replacement therapy in patients with ED and hypogonadism, ranging from 64% for primary hypogonadism to 44% for secondary hypogonadism. In another meta-analysis by my group, T treatments in hypogonadal men moderately improved the number of nocturnal erections, sexual thoughts and motivation, the number of successful intercourses, scores of erectile function, and the overall satisfaction compared with placebo; whereas
T had no effect on erectile function in eugonadal men. In this study, a cut-off T value of 288 ng/dl (10 nmol/l) failed to predict the effect of treatment. By contrast, the presence of risk factors for vasculogenic ED, comorbidities, and short evaluation periods were associated with greater T effects in hypogonadal but not in eugonadal men. Meta-regression analysis also showed that the effects of T on erectile function, but not libido, were inversely related to baseline T concentration.29

Given the multifactorial nature of the pathophysiology of ED, it is not expected that T monotherapy will be highly effective in the treatment of all patients with ED if baseline cut-off values are not chosen correctly. In general, T monotherapy for the treatment of ED is efficacious in men with hypogonadism when it is the sole cause of ED; but is often not efficacious in men with ED who show signs of hypogonadism and other comorbidities such as vascular disease and neuropathy.

Combination therapy and erectile dysfunction

Preclinical investigations reported by Traish et al.30 and Zhang et al.22 provided convincing evidence that PDE-5 inhibitors are ineffective in improving erectile function in androgen-deficient animals and that the re-administration of androgen facilitates PDE-5 inhibitor action. As already outlined, T may directly control the expression and activity of PDE-5 in human corpus cavernosum.13 Androgen deficiency or hypogonadism reduce the cavernosal expression of PDE-5 mRNA, protein, and enzyme activity, and T supplementation restores PDE-5 expression and activity,13,31 which represents the substrate for the inhibitory action of PDE-5 inhibitors.

The author was the first to investigate the effect of T on peripheral erectile mechanisms in a clinical setting. My group reported that plasma T concentration was related to erection entity as evaluated by duplex ultrasound scanning of the penis; in that study, 52 men with ED and no known vascular risk factors were investigated in a double-blind correlation analysis. We noted a direct correlation between corporeal resistive index values and free-T, a relationship that was maintained after adjusting for age, sex hormone-binding globulin (SHBG), level and estradiol level. We concluded that men with ED and low free T may have an impaired relaxation of the penile smooth muscle, thus providing clinical evidence for the importance of androgen in regulating erectile function.23 In a subsequent study, we performed a prospective, randomized, placebo-controlled pilot study in 20 men with ED in whom sildenafil 100 mg treatment failed on six consecutive attempts and had free T levels falling into the lower quartile of the lower range.26 One month after treatment with transdermal T patches and sildenafil on demand, we found significantly increased scores in the erectile function domain of the International Index of Erectile Function (IIEF). These clinical observations suggest a critical role for T in human erectile function. More importantly, in all patients there was a strong direct correlation between resistive index values and free T levels. Again, this relationship was maintained also when adjusted for age, SHBG level, and estradiol level. These results indicate that in men with ED, low free T may correlate independently of age with the impaired relaxation of the cavernous smooth muscle cells.

These findings were then confirmed by other authors’ clinical studies. Shamloul et al. have shown a similar enhanced response to sildenafil after T gel treatment in aging men;18 also, Greenstein et al. demonstrated that combined treatment with sildenafil and T gel has a beneficial effect on ED in hypogonadal patients in whom treatment with T supplement alone failed.13 The corollary has been shown that decreasing T levels impair the effectiveness of PDE-5 inhibitor treatment.14
In another randomized, placebo-controlled, double-blind, parallel-group, multicenter study, 75 hypogonadal or borderline hypogonadal men (18–80 years old) with confirmed lack of response to sildenafil monotherapy and morning serum total T of 400 ng/dl or less, were randomized to receive a daily dose of 1% T gel or 5 g placebo gel as adjunctive therapy to sildenafil 100 mg during a 12-week period. T-treated subjects had significant improvement in erectile function compared with those who received placebo. Similar trends were observed for improvements in orgasmic function, overall satisfaction, total IIEF score, and percentage of IIEF responders. The authors concluded that T-gel taken with sildenafil may be beneficial in improving erectile function in hypogonadal men with ED who are unresponsive to sildenafil alone. Greenstein et al. evaluated the efficacy of T gel alone in hypogonadal ED patients with comorbidities, reporting a beneficial effect on erection in most patients (63%); in the remaining patients, whose condition did not improve satisfactorily with T gel treatment alone, the addition of sildenafil brought normalization in erectile function scores.

Further striking evidence supporting combined therapy comes from the study by Rosenthal et al., who evaluated whether combination therapy with T gel and sildenafil was effective in achieving adequate potency in subjects with low-normal serum T levels. Despite the absence of a placebo arm, the study demonstrated that none of the men initially unresponsive to sildenafil alone, was supplemented with T alone, was able to achieve normal erectile function. Successive addition of sildenafil made most of the men (92%) capable of penetrating their partners during intercourse.

Furthermore, the efficacy of oral T preparations has been investigated by Hwang et al. in a series of hypogonadal patients unresponsive to sildenafil alone. One-third of hypogonadal patients with ED who failed to respond to sildenafil responded to T alone, and another one-third responded to sildenafil again after normalization of T. They concluded that in hypogonadal patients with ED, androgen supplementation represents the first-line therapy. Similar results were obtained by Kalinchenko et al. with an oral T preparation in reversing ED associated with type 2 diabetes in patients in whom sildenafil therapy alone had failed.

Other convincing evidence comes from clinical investigational studies in men with ED and chronic renal insufficiency-associated hypogonadism. In these men, intramuscular monthly injections of testosterone cypionate combined with oral sildenafil 50–100 mg once or twice weekly have been more successful than T alone, owing to the combined pathogenesis (i.e. vascular and hormonal), and such therapy may be beneficial in this group of patients. Similar results were reported by Tas et al. in a population of urologic patients unresponsive to T or erythropoietin alone. They concluded that the combination of erythropoietin plus sildenafil may salvage up to 50% of patients with ED while T treatment (alone or in combination with erythropoietin) would not be preferred in this population, owing to the possibility of fluid retention.

Finally, Yassin et al. investigated the efficacy of tadalafil in combination with T gel for the treatment of tadalafil-refractory ED in hypogonadal patients. They demonstrated that a combination therapy with T and tadalafil is an effective means in a subset of hypogonadal patients who do not respond to tadalafil alone in the long-term. T monotherapy effects were negligible at 4 weeks but became clinically relevant between 4 and 10 weeks of treatment and were similar to those obtained by combination therapy, thus suggesting that T-induced remodeling of penile tissue structure is a process that may require a longer period of T administration than 4 weeks. It can be argued that if patients are unresponsive to androgen alone or PDE-5 inhibitors alone, a prolonged combined use of both may improve erectile function, especially when ED has a multifactorial pathogenesis (Table 57.1).

Despite these clinical studies, the Endocrine Society have recently published a position paper in which a panel of experts concluded that very low-quality evidence exists in prescribing T therapy in older men with unequivocally low T levels for treating their ED, while this therapy remains an option in those men with lower T levels to improve libido. In the opinion of

<table>
<thead>
<tr>
<th>Authors</th>
<th>n/hypogonadism</th>
<th>PDE-5 inhibitor response at baseline</th>
<th>Efficacy/adverse events</th>
</tr>
</thead>
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<tr>
<td>Aversa et al.</td>
<td>20/No</td>
<td>Sildenafil failure</td>
<td>80%/none</td>
</tr>
<tr>
<td>Kalinchenko et al.</td>
<td>120/Yes</td>
<td>Sildenafil failure</td>
<td>70%/none</td>
</tr>
<tr>
<td>Shabsigh et al.</td>
<td>75/Yes</td>
<td>Sildenafil failure</td>
<td>70%/NA</td>
</tr>
<tr>
<td>Chatterjee et al.</td>
<td>12/Yes</td>
<td>NA</td>
<td>100%/none</td>
</tr>
<tr>
<td>Shamloul et al.</td>
<td>40/No</td>
<td>Sildenafil failure</td>
<td>Improved/none</td>
</tr>
<tr>
<td>Greenstein et al.</td>
<td>49/Yes</td>
<td>NA</td>
<td>63%/18% skin irritation</td>
</tr>
<tr>
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<td>32/Yes</td>
<td>Sildenafil failure</td>
<td>57%/none</td>
</tr>
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<td>Sildenafil failure</td>
<td>92%/1% headache</td>
</tr>
<tr>
<td>Tas et al.</td>
<td>23/Yes</td>
<td>NA</td>
<td>50%/none</td>
</tr>
<tr>
<td>Yassin et al.</td>
<td>69/Yes</td>
<td>Tadalafil failure</td>
<td>65%/none</td>
</tr>
<tr>
<td>Overall patients</td>
<td>428/368</td>
<td>70% failure</td>
<td>50–100%/1–18%</td>
</tr>
</tbody>
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PDE, phosphodiesterase; NA, not applicable.
the author, when serum T falls into the so-called uncertain zone (between 8 nmol/l and 13 nmol/l) and comorbidities are present in male ED outpatients, PDE-5 inhibitors represent first-line therapy for treating ED. However, higher rates of failure with PDE-5 inhibitors are reported in such cases, so that combination therapy may ‘salvage’ up to one-third of patients who would otherwise be candidates for investigative surgery procedures or penile implants. This approach has proven to be effective and safe in terms of overall satisfaction and intercourse satisfaction for the patients, without any long-term side-effects on prostate size and prostate-specific antigen (PSA) values in the hypogonadal patients. However, the lack of clinical trials designed to investigate the safety of this combination therapy in the long term means that this option cannot be recommended in large ED populations.

Figure 57.2 shows a proposed diagnostic flowchart for use during standard office evaluation of the patient not responding to PDE-5 inhibitors. In the opinion of the author, it is noteworthy that any treatment for ED should be initiated with T whenever clinical and biochemical T deficiency symptoms occur, whilst PDE-5 inhibitors are co-administered for immediate relief of the complaint of ED. In all remaining cases, a challenge with PDE-5 inhibitors alone is always recommended.

**Combination therapy and improvements in endothelial function**

Normal vascular endothelium is essential for the synthesis and release of substances affecting vascular tone (NO), cell adhesion (endothelins, interleukins), and the homeostasis of clotting and fibrinolysis (plasminogen inhibitors, von Willebrand factor). Endothelial dysfunction can be defined as an abnormal response leading to a reduction in the bioavailability of NO and impaired vasodilatation, and it plays a major role in the development of atherosclerosis and acute coronary syndromes and ED. The degeneration of endothelial integrity promotes adverse events leading to atherogenesis, such as infiltration of the vessel wall by macrophages loaded with oxidized lipoproteins.

Recent animal and *in vitro* studies have further documented that T up-regulates the expression of arterial AR mRNA and is associated with an inhibitory effect on neo-intimal plaque formation. T has a relatively rapid vasorelaxant effect in isolated rabbit coronary artery and aorta and porcine coronary artery. Other studies have suggested that T may play a role in vascular protection and remodeling responses to vascular injury by stimulating endothelial replication and inducing endothelium-dependent vascular relaxation. Additionally, positive acute hemodynamic effects of T on coronary vaso-motion and stress-test-induced ischemia were reported.

Nonetheless, interpretations of the effects of pharmacological doses of androgens on arterial compliance, and flow-mediated dilatation in particular, must also be treated with circumspection because, at physiological concentrations, beneficial, neutral, and detrimental effects on vascular reactivity can be observed.

Historically, the link between plasma T levels and increased risk of coronary artery disease (CAD) has been attributed, at least in part, to the unfavorable effect of the hormone on lipid metabolism and fibrinolysis. CAD represents one of the most common and costly atherogenic diseases in the Western world and is more common in men aged 30–50 years than in women.
of similar age; an observation that has often suggested harmful effects of androgens on the coronary circulation. Recent studies suggest that blood T concentrations are consistently lower among men with cardiovascular disease and angina and have demonstrated that T treatment may have beneficial effects on the coronary vasculature. Moreover, the presence of reduced T levels is associated with increased risk of CAD, visceral obesity, insulin resistance, low levels of high-density lipoprotein cholesterol (HDL-C), elevated triglycerides, elevated low-density lipoprotein cholesterol (LDL-C), and impaired plasminogen activator inhibitor (PAI) 1 and Lp(a) lipoprotein hemostasis. This is supported by reports that T replacement in males with idiopathic hypogonadotrophic hypogonadism is associated with decreased cardiovascular risk and that natural androgens may inhibit atherosclerosis in men.

The wide use of PDE-5 inhibitors by patients with ED and CAD yielded a considerable number of independent studies investigating the cardiovascular safety and functional role of PDE-5–cGMP–NO pathway in the cardiovascular system. However, such clinical studies have been conducted only with ‘on-demand’ modality of administration. Recent animal studies provide strong evidence for a direct protective effect of chronic PDE-5 inhibitor use against cardiomyocytes necrosis and apoptosis through an NO-signaling pathway mechanism. Ancillary studies from my group show an influence of 4 weeks of daily PDE-5 inhibitor administration on endothelial function in men with a wide ED etiology. In these studies, chronic PDE-5 inhibitor administration was able to improve both flow-mediated dilatation and surrogate markers of endothelial function, thus opening a new scenario for use of this class of drug. These promising results led my group to speculate about a possible synergistic effect of the combined use of T plus PDE-5 inhibitors in the treatment of many diseases associated with ED (CAD, diabetes, obesity) in which hypogonadism plays an important pathophysiological role.

Endothelial dysfunction is in turn associated with many of the risk factors for both CAD and ED (e.g. dyslipidemia, heart failure, diabetes mellitus, and cigarette smoking). Some of the drugs that have been shown to have a beneficial effect on morbidity and mortality in cardiovascular conditions such as the angiotensin converting enzyme inhibitors in heart failure and hydroxymethyl-glutaral co-enzyme A reductase inhibitors in ischemic heart disease, have additionally been shown to improve endothelial function. Furthermore, evidence is becoming available to suggest that measures of endothelial dysfunction might have value as prognostic factors for cardiovascular event rates.

In this view, emerging data are now providing convincing evidence that PDE-5 inhibitors may be used in a daily fashion to reverse endothelial dysfunction in patients with heart failure and patients with type 2 diabetes. A possible concern for tachyphylaxis with PDE-5 inhibitors has arisen with the suggestion that daily dosing may salvage poor responders to on-demand sildenafil therapy. Previous work with human cavernous smooth muscle cells in culture led to reports that tachyphylaxis could occur following repeated exposure to extremely high concentrations of sildenafil (25mM). Behr-Roussel et al. have hypothesized that chronic sildenafil treatment could help salvage poor responders to sildenafil therapy. Furthermore, because of its effect on the potentialization of endothelium-dependent cavernosal relaxations, chronic treatment with sildenafil could be of particular benefit in patients with CAD-related ED, in which cavernosal endothelial dysfunction occurs.

**Combination therapy and the prostate**

Even if T administration is proven to prevent or reverse the age-related declines in some functions, there is reason to wonder if it will also exacerbate T-dependent diseases to which elderly men are particularly prone. Giving T to the aging male with ED may sometimes cause an exacerbation of benign prostatic hyperplasia (BPH), a T-dependent disease. Symptoms, predominantly urinary outflow obstruction, may worsen. The symptom score should be assessed and, if warranted by the symptoms, the urine flow rate and the ultrasound post-void bladder residual urine should be measured.

Because prostate cancer is, at least to some degree, T-dependent, it seems theoretically likely that the risk of prostate cancer is less in hypogonadal men than eugonadal men and the risk increases to normal, but not above, when T is replaced. By contrast, it has been reported that prostate cancer may be more aggressive in hypogonadal men, so that a paradoxical protective effect of T administration can be hypothesized in those patients. It seems prudent, nonetheless, to screen hypogonadal men for prostate cancer before beginning T replacement and to monitor them for prostate cancer during treatment, just as one would monitor a eugonadal man. It has been demonstrated that serum T within the normal range is unrelated to prostate cancer incidence. Recently, a suggestion that intraprostatic androgen activity may increase and that serum estrogens may decrease the risk of prostate cancer occurrence has been raised, even if the contribution of each one remains unknown. Once T supplementation in hypogonadal patients is commenced, a PSA increase of ≥0.75 ng/ml per year over 2 years represents a biochemical marker for androgen supplementation withdrawal. For this reason, PSA may represent an indirect biochemical marker of androgenic function during replacement therapy and should be repeated at least every 3 months. As shown in Table 57.1, no serious treatment-emergent adverse events caused by combination therapy with T plus PDE-5 inhibitors in hypogonadal men with ED have been reported at the moment.

Another intriguing matter of debate is represented by the recent demonstration of positive immunostaining for NOS within the bladder and the prostate, which has raised the hypothesis of possible improvements in lower urinary tract symptoms (LUTS) following administration of PDE-5 inhibitors. The role of PDE-5 inhibitors for treating BPH is only poorly understood; reportedly, various PDE isoforms are expressed in the prostate and there are some clues that non-specific PDE inhibition can relax human prostate tissue. In an animal model of bladder outlet obstruction, it has been clearly shown that inhibition of PDE-5 leads to reduction of the irritative symptoms of BPH in vivo. Another pioneer animal study demonstrated that PDE-5 regulates bladder smooth muscle tone, strongly limiting the NO–cGMP signaling,
and that PDE-5 inhibitors may be a possible therapeutic option for bladder dysfunction by ameliorating irritative LUTS.\textsuperscript{66} Anecdotally some patients cite improvement in LUTS while using sildenafil. In a clinical study carried out in men with prostate symptom scores on the International Prostate Symptom Score (IPSS) >10, 60% of the men who were using sildenafil twice weekly for their ED also improved IPSS score, and 35% had at least a 4-point improvement in their score.\textsuperscript{67} The authors hypothesized that the effect of the medication might have been mediated through bladder neck or prostatic smooth muscle relaxation. Preliminary reports on the use of daily tadalafil in men with moderate-to-severe LUTS due to BPH have shown that after 6 and 12 weeks of treatment, a significant improvement of obstructive and irritative symptoms occurs when compared with placebo.\textsuperscript{68} If the reduction in prostate symptom scores was related to the improvement in obstructive symptoms, this would be in agreement with the anti-proliferative effect of PDE-5 inhibitors on prostate stromal cells.\textsuperscript{66} Taken together, these results open a new scenario for the patients using combination therapy with T and PDE-5 inhibitors, thus suggesting more benefits on the prostate and bladder outlet and obstruction symptoms after continuous use, even in the presence of mild BPH symptoms at baseline.

**Conclusion**

ED is extremely common and it is now well established that it can have a significant impact on the quality of life and self-esteem of sufferers. It is often associated with aging and can be a symptom of late-onset hypogonadism. Although low T levels do not necessarily cause ED and are not frequently reported in ED patients,\textsuperscript{69} a proportion of men (20–30\%) may not respond adequately to first-line treatment with PDE-5 inhibitors unless T levels are sufficient for intact penile machinery. Clinical trials have shown that T supplementation with newer preparations (intramuscular long-acting agents) can rapidly increase levels of T and improve sexual function and mood in men with hypogonadism.\textsuperscript{20} Currently there is no basis for large-scale T replacement therapy in older men, unless they have symptomatic T deficiency. However, identification of sub-populations who may benefit from T augmentation of PDE-5 inhibitor responsiveness may be clinically useful in order to maximize benefits other than sexual performance itself. The recent finding reporting that T replacement therapy reduces insulin resistance and improves glycemic control in hypogonadal men with type 2 diabetes\textsuperscript{74} is full of clinical extra-sexual implications. Accordingly, improvements in glycemic control, insulin resistance, cholesterol levels, and visceral adiposity together represent an overall reduction in cardiovascular risk that has been reported as an addition to benefits deriving from PDE-5 inhibitor daily use also. Altogether, these data need to be validated in large population-based studies.

Finally, it is mandatory that in the clinical setting, the age-related decline of serum T should be confirmed twice, along with measurement of SHBG. The bioavailable T (plasma or calculated) is currently not routinely recommended, owing to the many difficulties of measurement; however, the occurrence of free testosterone levels below 0.250 nmol/l may directly determine failure in men with ED in their clinical response to PDE-5 inhibitors so that its evaluation should always be performed. For these reasons, I do strongly recommend measurement of plasma T alterations in all ED patients, in order to verify the possibility of adding T-containing preparations if late-onset hypogonadism is diagnosed, and to maximize the effects of oral PDE-5 inhibitors, thus enabling successful treating of the sexual dysfunction.

**REFERENCES**

Augmentation of phosphodiesterase type-5 inhibitor response with testosterone 441


Phosphodiesterase type 5 inhibitors for the treatment of women’s sexual dysfunction

Salvatore Caruso, Agnello Carmela, and Lucia Di Mari

Introduction

Female sexual disorder (FSD) has been attracting much attention over the past few decades, producing new research in epidemiology, pathophysiology, and pharmacotherapy. This interest, paradoxically, was stimulated when scientific research defining the efficacy of sildenafil, an inhibitor of phosphodiesterase (PDE) type 5, a drug that was experimentally used in cardiology, but found 'by chance and unexpectedly' to cause side-effects, producing an erection in the test subjects.

This raised the question of whether a vascular medication such as a PDE-5 inhibitor could also be efficacious for FSD. However, there were some difficulties, namely the lack of definite diagnostic procedures, the lack of a widely accepted classification of FSD, as well as the anatomical aspects such as the biological mechanism of sexual excitement and of orgasm that were also not well defined. Moreover, it became increasingly evident that FSD can have an organic basis occurring secondarily to medical problems, even if risk factors for FSD are both psychological and physiological.

Consequently, FSDs have only recently gained the attention of medical research groups, who have begun to categorize it, defining possible etiologies for the problems and describing potential therapeutic approaches. Clinicians also began to consider a possible role for sildenafil in treating female sexual arousal disorder (FSAD).

Sildenafil revolutionized sexology, which had, until the 1990s, generally used only empirical treatment; in fact, the treatment for erectile dysfunction was often rudimentary and fundamentally the medical–surgical type, while psychotherapeutic methods were used for female sexual disorders.

The considerations that led to diametrically opposite treatment for men and women were based on clinical speculation, more or less scientific, since female sexuality had always been defined as more complex than that of males, the latter being considered simpler and more essential, based on coital capacity – the quality of the erection – and on the procreative capacity – the quality of seminal fluid, two aspects that are quantifiable and evident. The ignorance of female pathophysiology produced further difficulties in treatment, because it was easier to define female sexuality as being more complex and less accessible than male sexuality, and thus psychological. The heirs of the Freudian culture managed female sexology with the complicity of a medical community that was ignorant of the true female sexual physiopathology.

Historically the psychological and biomedical approaches were opposed, and sometimes they clashed. The former affirmed that it would be reductive to treat a woman affected by sexual dysfunction pharmacologically; the latter, instead, considered women’s problems as a therapeutic opportunity. On the other hand, today, sexual psychotherapists understand the importance of an integrative approach and try to use short-term therapy aimed at stimulating behavioral change.

The behavioral divergence in the field of the sexual life between men and women seems to be more subtle today. Men are now treated with drugs or psychotherapy for certain events that were once considered as being part of the female world only: fear, dyspareunia, hypoactive desire, and even headaches are just some of these problems. As a demonstration of how the somatic component can influence the generation of unease or sexual dysfunction, the most recent classifications focus on the concept of stress. According to these, a condition of ‘unease’ is considered a disorder whenever it produces stress for the woman who suffers from this condition.

In current concepts of FSD, there are both biomedical and physiological factors, among which are reduction in vaginal and clitoral blood flow, previous gynecological operations, alterations of the pelvic floor caused by childbirth, and disorders secondary to hormonal alterations. Magnetic resonance imaging has shown that during female sexual arousal changes occur in the anterior vaginal wall, through gradual filling of the bladder, and involving the clitoris. It is accepted that the clitoris plays a functional role during sexual arousal. All of these aspects make up the biological pathways that could be treated with drugs.

A better understanding of the structures and substances involved in normal sexual function, as well as age-related changes, can help practitioners to evaluate and appropriately manage women with FSD proactively. The continued quest to understand female sexual function and dysfunction requires more education and research on the treatment of underlying medical conditions and the use of pharmacologic therapies.

Sexual arousability largely depends on the sympathetic nervous system, and the non-adrenergic/non-cholinergic (NANC) neurotransmitters [i.e. vasoactive intestinal polypeptide (VIP) and nitric oxide (NO)] are involved in smooth
muscle relaxation and enhancement of genital blood flow, while various hormones may influence female sexual function.10–22

Today there are no drugs approved for the treatment of FSD,23 though there have been independent studies and studies supported by pharmaceutical companies to look at the efficacy and safety of drugs that act on peripheral or central sexual pathways. To date, among the known PDE-5 inhibitors, sildenafil has been the most studied drug to treat FSAD. Thus sildenafil is used here to stand for the category of PDE-5 inhibitors.

Sildenafil and female sexual arousal disorder

The introduction of sildenafil44 for the treatment of men affected by erectile dysfunction represented a major advance in the understanding and management of the neurovascular mechanisms of sexual response. In the female corpus cavernosum, the release of NO from the NANC nerves or the endothelium activates guanylyl cyclase and increases intracellular cGMP levels. cGMP modulates intracellular calcium and, in turn, regulates smooth muscle contractility and erectile function.21 PDE-5 plays an important physiological role by regulating the intracellular levels of cyclic nucleotides.25 Sildenafil is able to inhibit cGMP hydrolysis by high-affinity selective PDE-5 inhibition in intact cells and in soluble extracts of human clitoral corpus cavernosum smooth muscle cells.26 PDE-5 has also been found in clitoral and vaginal tissue.27,28

Clinical trials suggest that sildenafil could be an effective treatment for iatrogenic sexual dysfunction,29,30 on the basis of the observations that human clitoral corpus cavernosum smooth muscle tone may be regulated by synthesis and release of NO,21 and that this pathway is dependent on PDE-5 activity. Researchers in the sexual field have hypothesized that sildenafil could have beneficial clinical effects on women affected by sexual arousal disorders. In a clinical setting, sildenafil was shown to enhance genital blood flow and vaginal and clitoral engorgement in women affected by FSAD. Several studies have been performed over the past few years, in premenopausal or postmenopausal women with FSAD, and in healthy women without sexual dysfunction in order to study female sexual pathways, and finally, on subjects with psychotropic-induced sexual dysfunction, and on premenopausal women with diabetic-induced FSAD. A closer examination of these studies follows, and they are summarized in Table 58.1.

Premenopausal studies

A pilot study on the effect of sildenafil on subjective and physiologic parameters of the female sexual response evaluated its safety and efficacy for use in women with FSAD.32 Physiologic measurements, including genital blood flow, vaginal lubrication, intravaginal pressure–volume changes, and genital sensation, were recorded before and after sexual stimulation at baseline and following administration of sildenafil 100 mg. Post-stimulation physiologic measurements showed significant improvements. Subjective complaints of sexual function, including low arousal, low desire, low sexual satisfaction, difficulty in achieving orgasm, decreased vaginal lubrication, and dyspareunia, also improved significantly.

The major findings of a double-blind, cross-over, placebo-controlled study in premenopausal women with normal ovulatory cycles and normal levels of steroid hormones, affected by FSAD but without hypoactive sexual desire disorder (HSDD) were that subjects may benefit from treatment with sildenafil, showing improvements in arousal and, indirectly, in orgasm, and in frequency and enjoyment of sexual intercourse.23 The various hormonal levels could explain the differences in the results from other studies in postmenopausal women, which have shown little or no improvement. These negative results could be due to the low ovarian steroid levels that first need to be treated before beginning sildenafil therapy.

Postmenopausal studies

Another open-label, non-randomized study in postmenopausal women with sexual dysfunction, based on history, found that, overall, only 18.1% had a significant therapeutic response to sildenafil, while clitoral discomfort and hyper-sensitivity occurred in 21%.34 Side-effects included headache, dizziness, and dyspepsia. The data suggest that sildenafil is well tolerated in postmenopausal women with sexual dysfunction, but overall sexual function did not improve significantly, although there were changes in vaginal lubrication and clitoral sensitivity. It should be noted that insufficient vaginal engorge-ment and insufficient clitoral erectile function in postmeno-}


thus, sexual arousal in these women, and other aspects of female androgen-dependent sexuality, are unlikely to be improved by treatment with sildenafil.

Sildenafil efficacy in postmenopausal women with FSAD who either had normal estradiol and free testosterone concentrations or were receiving estrogen or androgen replacement therapy (or both) was studied in a double-blind, placebo-controlled trial. Women with FSAD without HSDD had a significantly greater improvement in sexual arousal, orgasm, intercourse satisfaction, and overall satisfaction with their sexual life during sildenafil intake compared with those taking placebo, while no efficacy was shown for women with concomitant HSDD.

### Efficacy studies in healthy women

To determine changes in female sexual pathways caused by sildenafil, and to verify the safety of the drug, a randomized, double-blind cross-over, placebo-controlled study was conducted in premenopausal women asymptomatic for sexual disorders, with normal ovulatory cycles and with normal steroid levels. Sildenafil improved arousal, orgasm, and enjoyment compared with placebo. The major findings of the study were that sildenafil can improve general sexual behavior. The benefits that the sildenafil group felt were mainly in the vagina and clitoris, confirming the peripheral genital target of PDE-5 inhibitors. This study thus showed that both the qualitative (arousal, satisfaction and orgasm) and quantitative (multiple orgasm) aspects of sexuality are significantly improved with respect to the pre-test baseline values. The majority of the adverse events associated with the use of sildenafil were related to vasodilatation (such as headache), gastrointestinal events (with nausea), or to minor visual effects. Each of these adverse effects reflects the well-known pharmacological properties of sildenafil, and they usually increase in incidence with increasing drug dose. The study suggested that sildenafil acts on different sexual pathways in healthy women, improving their sexual experience; when sildenafil was given to these healthy women having a normal vasodilatory function, the PDE-5 inhibitor increased this activity.

Sildenafil was also found to be effective in enhancing vaginal engorgement during erotic stimulus conditions in healthy women without sexual dysfunction but it was not associated with an effect on subjective sexual arousal. Women without sexual dysfunction were randomly assigned to receive either sildenafil or placebo. Subjective measurements of sexual
arousal were assessed after participants had been exposed to erotic stimuli. Vaginal vasocongestion was recorded continuously during baseline, neutral, and erotic stimuli. At the end of each session, subjects were also asked to specify which treatment they suspected they had received. Significant increases in vaginal vasocongestion were found with sildenafil treatment compared with placebo. There were no differences between treatments on subjective sexual arousal experience. Analyses by ‘suspected treatment received’ found that significantly stronger sexual arousal and vaginal wetness were reported for the treatment that was believed to be sildenafil.

**Women with psychotropic-induced sexual dysfunction**

Women reported significant improvements in all domains of sexual functioning and in overall sexual satisfaction after sildenafil treatment. Significant improvements were reported regardless of psychotropic medication type. However, patients taking selective serotonin reuptake inhibitors reported less improvement in arousal, libido, and overall sexual satisfaction than did other patients, whereas patients taking benzodiazepines reported significantly more improvement in libido and overall sexual satisfaction.

Patients who had normal premorbid sexual function and who had developed sexual dysfunction, particularly anorgasmia, with or without other sexual disturbances (i.e. loss of libido, lubrication difficulties, uncomfortable or painful intercourse) while being effectively treated with an antidepressant or mood stabilizer were treated with sildenafil. The subjects showed improvement in the presenting condition, usually depression, anxiety, or both. Patients took sildenafil and reported a complete or very significant reversal of their sexual dysfunction. This included return of effective duration and intensity of adequate arousal, lubrication, and orgasmic function.

**Diabetic women with seasonal affective disorder**

The sexual function of women with diabetes has received little attention in clinical research even though diabetes has recently been shown to increase the risk of female sexual dysfunction. Changes in sexual genital pathways, such as diminished clitoral sensation, vaginal dryness, vaginal discomfort, orgasmic dysfunction, and dyspareunia, might be the mechanisms that cause damage to the vascular and autonomic nervous systems, as well as causing alterations in the production and efficacy of NO. The most commonly reported sexual problem in women with diabetes is genital arousal disorder. To date, only two studies have been performed with diabetic women affected by FSAD, using sildenafil, the results of which are reported below.

A study was performed to verify whether sildenafil was effective in modifying clitoral blood flow in premenopausal diabetic women. Thirty women affected by type 1 diabetes treated with insulin therapy participated in a prospective open-label clinical study. Each woman received a single oral dose of sildenafil 100 mg. Translabial color Doppler ultrasonography was used to measure the resistance index, pulsatility index, peak systolic velocity, and end-diastolic velocity of the clitoral arteries 1 hour and 4 hours after sildenafil administration. One hour after the drug intake, the mean resistance index was significantly lower and the mean pulsatility index, mean peak systolic velocity, and mean end-diastolic velocity of the clitoral arteries were significantly greater compared with both the baseline readings and the readings 4 hours after sildenafil. These hemodynamic changes observed sonographically showed that sildenafil is able to improve the clitoral blood flow of premenopausal women with type 1 diabetes.

The results obtained from this study led to a second prospective study, which had a double-blind, cross-over, placebo-controlled design. Thirty-two premenopausal type 1 diabetic women affected by FSAD participated in the study. Efficacy was assessed subjectively to quantify arousal, desire, orgasm, enjoyment of sexual activities, and frequency of sexual relationships; and objectively by translabial color Doppler ultrasound to measure the changes in clitoral arteries. Flowmetric values of the clitoral arteries were significantly higher compared with baseline and placebo.

**Conclusion**

FSD is a combination of problems with both biological and psychological components. It is multifactorial in etiology and includes couple problems and behavioral, and sociocultural aspects.

Sildenafil seems to be more effective in premenopausal women with FSAD than in postmenopausal women. This could be explained by the important role played by sexual steroids in genital trophism. In fact, the best response to sildenafil was in women affected by genital arousal dysfunction. From these studies, it can be seen that women with other sexual dysfunctions, such as HSDD, do not benefit from sildenafil. Consequently, defining specific subgroups of women is the first step in treating this dysfunction.

From the studies that have been carried out using PDE-5 inhibitors, it can be seen that these drugs are potentially useful in treating women with FSAD. We are at the beginning of a new era in treating FSD, and the development of new drugs in this field can only improve the situation.

There are currently potential therapeutic options for the treatment of FSD, including both hormonal and non-hormonal pharmacological therapies. However, sex therapists are discovering that integrating adjunctive use of drugs with sex therapy can accelerate the therapeutic process and improve outcome. As new pharmaceuticals are developed and approved for women, opportunities for medical and non-medical sex therapies will increase. To date, the results of the studies on women affected by sexual dysfunction who received drug treatments are still discordant, and this could be a result of the multifactorial aspects of female sexual dysfunction. Specific subgroups obviously need to be diagnosed for the treatment of female dysfunctions. Finally, we are beginning to consider sexual dysfunction treatment in an integrative setting, rather than symptomatic therapy, so that more recent drugs, such as PDE-5 inhibitors, may be useful.


Erectile dysfunction and diabetes
Suks Minhas, Ian Eardley, and Michael G Kirby

Introduction
Diabetes mellitus is the single most common cause of erectile dysfunction (ED) seen in clinical practice, with up to 28% of men attending an ED clinic presenting with diabetes. The association between diabetes and ED was first documented by Rollo in 1798 and, although some of the mechanisms by which diabetes leads to ED remain unclear, a number of factors appear to be involved, of which vascular and neuronal factors are probably the most important.

Epidemiology
Around 50% of men with diabetes have ED. In most, the problem develops during the course of the disease but, in a small proportion, it may be the presenting feature. Indeed, in one study of 497 men who had been referred for assessment of their ED, 11.1% were found to suffer from undiagnosed diabetes mellitus while a further 4.2% had impaired glucose tolerance. Performing a fasting glucose is the most reliable way to detect asymptomatic diabetes.

Although there is some evidence that patients with diet-controlled diabetes are less likely to develop ED, most reports suggest that there is no difference in incidence between those who are treated with oral hypoglycemics and those who require insulin. In those men who do develop ED, the onset is associated with increasing age, the duration of the diabetes, and the development of other complications, of which microangiopathy and neuropathy are the most important. The most usual clinical indicator of microangiopathy used in these studies was retinopathy, while symptomatic autonomic neuropathy was found to be more closely associated with the development of ED than was peripheral sensory neuropathy.

It has also been suggested that the likelihood of developing ED is directly related to the degree of glycemic control; for instance, one study demonstrated a definite association between ED and the level of the glycosylated hemoglobin. Other factors that appear to increase the risk of ED in diabetic subjects include alcohol intake and the use of antihypertensive medication.

Pathophysiology
The roles of neuropathy and vasculopathy in the etiology of diabetic ED are well recognized and are discussed below. Historically, it was considered that diabetes led to gonadal dysfunction with associated endocrine abnormalities, and that this contributed to the pathophysiology of the condition. Murray showed that testosterone levels were lower in men with diabetes and he also showed that testosterone therapy improved the ED, but only in those men who did not have severe vascular disease. The Rancho Bernado Study followed up 985 men and reported on 110 of the men who also had diabetes. The incidence of hypogonadism in these men with diabetes was 21%, whereas the incidence in the general population was 13%. A further study reported a prevalence of secondary hypogonadism of 33%, in a cohort of men with type 2 diabetes.

Currently, attention is increasingly being focused on the role of the vascular endothelium and the control of smooth muscle tone within the penis. There is increasing evidence that diabetes leads to abnormal endothelial and smooth muscle function throughout the body and that, in the penis, this can lead to ED.

Animal models of erectile dysfunction and diabetes
There are a number of models of diabetic ED but only four have been used to any extent in the study of diabetic ED. First, diabetes may be induced by the intravenous or intraperitoneal injection of streptozotocin so that diabetes develops within 8–14 weeks. In studying diabetic impotence, the streptozotocin has usually been administered to rats, with indicators such as weight loss, glycosuria, and an increase in the serum blood sugar confirming the development of diabetes. Similarly, diabetes may also be induced (usually in rabbits) by the intravenous injection of alloxan. Two rat models in which the rat is genetically predisposed to develop diabetes (the BB rat, which is insulin-dependent, and the BBZ rat, which is insulin-independent) have also been used to study ED in diabetes.

Although animal models are an imperfect means of understanding any human disease, for the purpose of studying the physiology and pharmacology of erection and the pathophysiology of a condition such as diabetic impotence, they are invaluable. Corporal tissue from both potent men and from diabetic men (both potent and impotent) is often difficult to obtain and the models outlined above at least provide tissue for study in the laboratory. However, there are a number of problems: for instance, some of the animals have uncontrolled and untreated hyperglycemia, which does not directly relate to the human situation, in which treatment with insulin or
with oral hypoglycemic agents is usual. Secondly, clinical diabetes is a chronic condition and the animal models are largely acute diabetic models. It is unclear exactly what effect the duration of the hyperglycemia has on the results obtained in experimental studies. Finally, the animal models described above are all different, and it is not clear what their relationship is with each other, let alone what their relationship is with human physiology and pathophysiology.

Despite these disadvantages, animal models continue to be integral to the investigation of diabetic ED, and in the future it will be vital that both the similarities and the differences between the different animal models are identified, together with the relevance of the animal models to the human situation.

**Neurogenic factors**

There is considerable evidence to suggest that the development of neuropathy in men with diabetes might have a role in the subsequent development of ED. The neuropathy seen in diabetes initially affects small unmyelinated fibers, and this, in turn, can lead to functional abnormalities in a number of organ systems: for instance, there may be postural hypotension and disorders of the gastrointestinal tract, while peripherally there may be disordered thermal sensation and abnormalities of sweating. In the later stages of the disease, larger myelinated fibers are also affected, with the longest fibers usually being affected first. This produces the classical ‘glove-and-stocking’ distribution of the peripheral neuropathy.

Morphological evidence from both human tissue and from diabetic animal models has usually demonstrated changes in innervation. In diabetic rats, a reduction in the size of the myelinated nerve fibers, together with accumulation of glyco- gen in axons and lipid droplets in Schwann cells, has been demonstrated in the dorsal nerve, although no changes were noted within the cavernous nerve.13 Human studies have provided conflicting evidence: whereas both light microscopy and electron microscopy have demonstrated changes in the nerves of the corpus cavernosum in some groups,14-16 these changes have not been demonstrated in other groups.17

At a cellular level, the bulk of the evidence, both in humans and in animal models, seems to suggest depletion of neurotransmitters. Early qualitative studies in both humans and rats demonstrated both reduced vasoactive intestinal polypeptide (VIP) and reduced acetylcholinesterase immunoreactivity.18,19 Later studies have usually demonstrated reduced VIP and nitric oxide synthase (NOS) immunoreactivity, both in experimental animals and in humans,20,21 although two reports in the streptozotocin rat have appeared to contradict these findings.22,23 These differences may simply reflect the different tissues being used and, in particular, the duration of the diabetes. However, it is interesting that, although the levels of VIP were increased in the penis and major pelvic ganglia of the diabetic rat, intracavernous injection of VIP induced erections in control rats but not in diabetic rats, suggesting an abnormality at the receptor level.22 A reduction in noradrenaline levels in both animal and human erectile tissue has also been demonstrated,24,25 suggesting that any neuropathy may affect sympathetic as well as the parasympathetic nerve fibers.

In clinical studies, a number of groups have investigated neurophysiological changes in patients with diabetes. The most usual measure has been the latency of the bulbocavernosus reflex (BCR), whereby a response is measured electrically in a muscle of the pelvic floor such as the striated urethral sphincter or the bulbocavernous muscle itself, following electrical stimulation of the dorsum of the penis or occasionally of the bladder neck. The reflex is known to be polysynaptic, with both somatic afferents (when the dorsal nerve of the penis is stimulated) and efferents (the pudendal nerve). Using this technique, abnormal BCR latencies have been demonstrated in up to 50% of patients.24-26 However, when taken as a group, some studies have shown no difference from control values27 and most have concluded that the BCR has little role in the diagnosis of neuropathic ED in men with diabetes.26,29

The fundamental problem with the BCR (and other tests of the sacral reflex latency) is that it measures conduction in large myelinated fibers, whereas the autonomic neuropathy of diabetes primarily affects the small unmyelinated nerves and affects the larger fibers only relatively late in the disease. Accordingly, there will always be a proportion of men with diabetic autonomic neuropathy who will have normal BCR latencies. This means that the BCR has little diagnostic accuracy in this respect and, indeed, is a marker only of relatively severe neuropathy.

A number of approaches have been tried to resolve this problem. One variation of the BCR is to stimulate the vesico- urethral junction with a catheter-mounted stimulating electrode. This approach stimulates small unmyelinated afferent nerves, and an electrical response can be recorded in the pelvic floor. Using this technique it was found that 66% of men with diabetes and ED exhibited abnormal responses and, as a group, there was a significant difference from control values.30 Other groups have tested for thermal threshold (which assesses small unmyelinated cutaneous nerve fibers) either on penile skin31 or on the sole of the foot,32 and both have been claimed to be a much more sensitive indicator of neuropathic ED in men with diabetes. Finally, the use of corpus cavernosum electromyography, if it really does record cavernosal smooth muscle activity, may also provide evidence about neuropathy and diabetic ED.27,32

**Vascular factors**

The penis is a vascular organ. Increased arterial inflow and relaxation of the smooth muscle lining the sinusoidal spaces is fundamental to the process of penile erection. Factors that impede blood flow into the penile helicine vessels and sinusoidal spaces will lead to ED. Diabetes mellitus is associated both with atherosclerosis in large arteries (which appears more frequently and at an earlier age than in non-diabetics) and with a microangiopathy, characterized by increased thickening of the capillary basement membrane.

Arteriography has demonstrated that stenosis of the internal pudendal artery is more common in impotent than in potent diabetics,33 and duplex ultrasound scanning of the penile arteries has shown that, in impotent men, diabetes is associated with a smaller penile artery diameter and lower peak flow velocities following injection of an intracorporal vasoactive agent.31,34,35 Morphological studies of diabetic tissue
have demonstrated ultrastructural changes within small penile vessels, including endothelial proliferation, subintimal fibrosis, and endarteritis obliterans. Recently, endothelial injury, as well as morphological changes in the smooth muscle cells, have been documented in diabetic rabbits, while, in the same animal model, a direct correlation between smooth muscle fibrosis and the degree of hyperglycemia has been demonstrated. The fibrosis was thought to be consistent with a vascular lesion.

Clinical studies have clearly demonstrated a close correlation between diabetic ED and other manifestations of diabetic vascular disease – namely, retinopathy, intermittent claudication, and the risk of amputation.

Diabetes is also associated with other conditions that can cause vascular problems. For instance, there is an increased risk of both hypercholesterolemia and hypercoagulability. Hypercholesterolemia is a risk factor for impotence in its own right and also leads to an increased risk of atherosclerosis. At a cellular level it can lead to increased contractility and impaired endothelium-dependent relaxation of the cavernosal smooth muscle, both of which have been demonstrated in animal models of hypercholesterolemia. The hypercoagulability associated with diabetes is secondary to an increase in coagulation factors such as factor IX (von Willebrand factor) and tissue plasminogen activator, which in turn can lead to subsequent vessel thrombosis and reduced vascular inflow.

The recognition of ED as a warning sign of silent vascular disease has led to the concept that a man with ED and no cardiac symptoms is a cardiac (or vascular) patient until proven otherwise.

**Endothelial and smooth muscle factors**

The endothelium lining the lacunar spaces is important in controlling corporal smooth muscle tone. Nitric oxide, constrictor prostanooids, and endothelins are all produced by the endothelium and act directly on the smooth muscle cell. In diabetes, impaired neurogenic and endothelium-dependent smooth muscle relaxation in response to acetylcholine has been demonstrated in both animal and human studies of penile erection. In one diabetic rat model there was reduced soluble nitric oxide synthase (NOS) activity in the penis together with reduced neuronal NOS.

In another human study there was reduced NOS immunoreactivity within the nerves of the penis affected by diabetes. However, increased NOS activity has been demonstrated in the corpus cavernosum of another diabetic rat model, whereas increased numbers of NOS-binding sites have been demonstrated in this rat model. With evidence that NOS is impaired in the penis of the diabetic rabbit, the situation is most confused.

It seems that diabetes may lead to depletion of the neuronal NOS with other effects upon the endothelial NOS, but why is both neuronal and endothelial-dependent relaxation of the cavernosal smooth muscle impaired? There are a number of possible explanations for this and, as is often the case, several of them may ultimately prove to be important. It has been suggested that a simple rise in the blood sugar may mediate these changes. Certainly, in vitro experiments in other tissues have demonstrated an augmentation of the contractile response to adrenergic agonists and a reduced relaxation response to nitric oxide upon exposure to hyperglycemia.

Initial studies in rabbit corporal tissue have provided similar findings, and it may be that some of these effects are due to an increased production of constrictor prostanooids.

Oxygen free radicals (such as the superoxide anion) have a role in producing impaired cavernosal relaxation. It is known that free radicals are able to inactivate nitric oxide and regulate smooth muscle tone in some tissues and it has been proposed that, in diabetes, increased auto-oxidation of glucose results in overproduction of free radical species, which in turn leads to smooth muscle dysfunction.

Interestingly, the impaired endothelium-dependent relaxation seen in diabetic vascular tissues is reversed by the addition of superoxide dismutase, which is able to inactivate the superoxide anion. The polyol pathway is also involved in the pathogenesis of hyperglycemia-induced changes of vascular endothelium and smooth muscle function. In hyperglycemia, induction of the enzyme aldose reductase leads to an increased production of sorbitol, which in turn causes an increased consumption of NAD(P)H, which is an essential cofactor in the production of nitric oxide. Although it has been proved that this is important in the diabetic rat aorta, as yet it has not been confirmed in penile erectile tissue from either experimental animals or humans.

Advanced glycosylation end-products (AGES) have an important pathophysiological role in the complications of diabetes mellitus. AGES are compounds that are formed as a result of non-enzymatic reaction between glucose and the amino groups of long-lived tissue proteins such as collagen. They are found to occur in increasing amounts not only in association with diabetes but also with aging. Amongst their various pathological effects has been demonstrated an ability to bind (or ‘quench’) nitric oxide, at least in animal models including corpus cavernosum. AGES have now been demonstrated in both human corpus cavernosum and tunica albuginea and, as noted above, have been found to increase with age.

However, a simple reduction in mediators of smooth muscle relaxation, as would be produced by any of the above explanations, may provide only part of the story. Certainly, one group of investigators has demonstrated an increase in endothelin-1 binding in the diabetic rabbit penis and has suggested that this may represent a possible pathophysiological mechanism of the ED seen in diabetes. Others have demonstrated an increased sensitivity of human diabetic smooth muscle cells to alpha-adrenergic agonists, and it may be that, in diabetes, there is heightened contractility as well as decreased relaxation of the corporal smooth muscle. It also seems clear that the vascular and sinusoidal endothelium has a central role in the modulation of this process.

An extensive review of the literature has shown that elevated blood sugar may cause regional hemodynamic changes, particularly endothelial-dependent relaxation. Protein kinase C becomes activated and nitric oxide is inactivated by the generation of oxygen radicals, which cause injury to the endothelial cells. This has been studied in patients with poorly controlled diabetes, and those patients whose glycosylated hemoglobin levels decreased from 10.2% to 8.2% noted a...
non-significant improvement over the short term in endothelial activation and fibrinolysis.69

Free radicals can be produced when endothelial function is abnormal and it has been shown that hypoglycemia induces significant levels of free oxygen radicals.70 Poor control of diabetes leads to glycosylated hemoglobin-generated superoxide anions, which decrease the production and bioavailability of endothelial and neuronal nitric oxide.71

Endocrine factors

Both erectile function and sexual physiology are reliant upon a normal endocrine milieu that is provided by a normally functioning pituitary, hypothalamus, adrenal gland and testis. An early study suggested both that hypogonadism was common in diabetes and that treatment with testosterone was effective.72 A number of studies have demonstrated that diabetes may be associated with diminished levels of serum testosterone as well as impairment in testicular function. For instance, it was shown that there were decreased serum free testosterone levels in men with diabetes and primary organic ED compared with both normal men and diabetic men with primary psychogenic ED.67 This study also demonstrated increased urinary excretion of luteinizing hormone (LH), although the serum LH level was similar in all groups. Those authors also reported improved sexual function, both subjectively and as assessed by nocturnal penile tumescence (NPT) studies following therapy with parenteral testosterone. Finally, studies in diabetic rats demonstrated both a reduced serum testosterone70,72 and a reduction in size of androgen-sensitive accessory reproductive organs.72

Treatment of the low levels of testosterone that are often discovered in patients with diabetes may correct many of the symptoms of androgen deficiency and may improve ED. This, however, will depend on how many other comorbidities are present, especially in terms of vascular disease. A study involving the treatment of hypogonadism in men with diabetes using testosterone undecanoate 120mg daily for 3 months showed that androgen replacement had a positive effect on visceral obesity, body weight, waist–hip ratio, and body fat. In addition to this, there was improved metabolic control and a fall in glycosylated hemoglobin from 10.4% to 8.6%, and there was a reversal in the symptoms of androgen deficiency, including an improvement in erectile function.73

Sildenafil has been found to be more effective in diabetic men when the diabetes is well controlled. In a study of men with diabetes there was a 64% success rate when their levels of glycosylated hemoglobin were less than 9% and a 44% success rate when the levels were greater than 9%. Additionally, neuropathy in men with diabetes but with good glucose control also reduced the success rate to 50%.74

Psychogenic factors

Although the majority of men with diabetes will probably have primarily an organic component to their ED, a number may have additional psychological factors. In fact, in a number of studies, some of which have used NPT to identify organic ED, up to 30% of diabetic men with ED have been found to have significant psychogenic problems that contributed to their ED.75–77 In the majority of cases these were secondary to the organic problems but in a significant proportion the psychogenic factors were the most important.76

Summary

In most patients with diabetic ED there will be a number of pathophysiological mechanisms at work and the relative importance of these factors will vary between patients. Whereas neuropathy, endocrinopathy, and atherosclerosis are undoubtedly important in a proportion, it is becoming increasingly evident that endothelial and smooth muscle function is disordered in diabetes and that this may be the most important factor for the majority of men.

Management of erectile dysfunction in patients with diabetes

Clinical features

The clinical assessment of men with diabetes ED is similar to the assessment of other men with ED. Although ED is occasionally the presenting symptom of undiagnosed diabetes, in the majority the diabetes has already been diagnosed. It is important not to miss other potentially important etiological factors, some of which may be associated with diabetes. For instance, if the patient is also hypertensive it is possible that the antihypertensive medication may be contributing to the ED.

Clinical experience confirms that certain antihypertensive drugs not only affect the blood pressure but also the compliance of the erectile tissue, resulting in a functional venous leak. This may impair erectile function as much as the arteriosclerotic changes of the vascular system secondary to hypertension.78 Fogari et al. compared the effect of antihypertensive treatment with valsartan versus carvedilol on sexual activity in 120 hypertensive men in a randomized, crossover study.79 Erectile dysfunction was spontaneously complained of by 15 patients in the carvedilol group and only 1 patient in the valsartan group.

The angiotensin receptor blocking drugs are the drug of choice in hypertensive patients suffering from ED. In 1998 the advent of the phosphodiesterase (PDE) type 5 inhibitors revolutionized the treatment of ED, especially in men suffering from diabetes. The PDE-5 inhibitors reduced the breakdown of cGMP to GMP, which prolongs vasodilatation. cGMP is produced from nitric oxide, which in turn is produced from the endothelium and also from the non-A–non-C nerve fibers. In patients with diabetes, the production of nitric oxide by the non-A–non-C fibers will be decreased, because they have diabetic neuropathy. No head-to-head studies of PDE-5 inhibitors have been done in a diabetic population.80

Although the physical examination often contributes very little to patient management, it does provide an opportunity to identify other diabetic complications and to form an opinion about whether there are prominent vascular or neurological components to the development of ED. For instance, diabetic retinopathy appears to correlate directly with the presence of ED,66,67 while evidence of peripheral vascular disease
with loss of peripheral pulses and intermittent claudication suggests significant large-vessel disease. The neurological examination may identify a peripheral sensory neuropathy, which typically has a glove-and-stocking distribution and which initially affects the small unmyelinated fibers that mediate vibration. Finally, there may be postural hypotension, indicative of an autonomic neuropathy.

The quality of diabetic control should be assessed, by performing a random blood sugar and a glycosylated hemoglobin test, particularly since the quality of the diabetic control seems to be a significant risk factor in the development of diabetic ED. Blood lipids and blood pressure should also be reviewed. Given the possible increased risk of hypogonadism, serum testosterone should be checked, together with thyroid function.

Treatment

The PDE-5 inhibitors are first-line therapy and more efficacious when diabetic control is good. Vardenafil has been studied in patients with diabetes, including those with neuropathy (sildenafil failures were excluded). Sixty-four percent of the men were able to penetrate their partners and 54% to complete intercourse, versus 36% and 23%, respectively, for the placebo group.

Tadalafil has also been studied in men with diabetes and ED. Patients had mainly moderate to severe ED, but did include men with neuropathy and retinopathy. The drug was less efficacious than in non-diabetic patients. There was a percentage improvement over baseline, with the ability to penetrate increasing – 22.6% vs 4% for placebo. The results for tadalafil in patients with diabetes have been pooled, giving a total of 637 men with diabetes. The results were compared with those of 1681 men without diabetes. The baseline from the International Index of Erectile Function (IIEF) scores in the erectile function domain confirmed that men with diabetes had more severe ED (12.6 vs 15); however, the diabetic men who received tadalafil had a mean improvement in the IIEF score of 7.4 compared with 0.9 for those men in the placebo group.

The baseline IIEF scores correlated inversely with the control of diabetes as measured by glycosylated hemoglobin. There have also been good results with sildenafil versus placebo in men with diabetes. As with all PDE-5 inhibitors, the results are not quite as good as in the pivotal trials in a general population.

Because this is a difficult group to treat, other therapies for ED may be required, including intraurethral alprostadil, penile self-injection therapy, vacuum constriction devices, and, as a last resort, penile prosthesis.

Intracorporal injection therapy

Many diabetic men will respond to intracorporal injection therapy. The standard primary agent is prostaglandin E-1 (PGE-1), although papaverine is also effective in many men. In men with prominent neuropathy, relatively small doses of both agents are effective, whereas in men with severe vascular disease large doses may be needed and, indeed, combination therapy may be required. PGE-1 can usefully be combined with either papaverine or phentolamine, or both, although in a small proportion of men there is no response, even at maximal doses.

It can be argued that patients with diabetes are likely to comply better with injection therapy than many other patient groups: first, they are often young men who are well motivated; second, a significant proportion will already be self-injecting with insulin. However, it also seems that patients with diabetes are less likely to respond to injection therapy. In one study, using PGE-1 as monotherapy, only 52% of diabetic men responded successfully to injection therapy, and in another study, using papaverine monotherapy, only 61% of men responded. Finally, in a third study, using a papaverine–phentolamine combination, 21 of 35 diabetic patients with ED failed to get a satisfactory response. Interestingly, there was no difference in neurological, vascular, or drug-related risk factors between those patients who responded and those who did not. There was, however, a correlation with the age of the patient, in that younger men tended to respond better to injection therapy.

Complications of injection therapy in diabetic patients are similar to those seen in the general ED population. However, there is potentially an increased risk of infection and occasional rare cases of sepsis have been reported in patients with diabetes following injection therapy. In addition, it has recently been reported that pain at the site of injection may be more problematic in these patients and particularly in those who use high doses of PGE-1.

For patients who have pain with PGE-1 injection, a combination of vasoactive intestinal peptide and phentolamine can be tried. An alprostadil preparation using transurethral application with a small single-use applicator was introduced in 1994 and marketed as MUSE (Medicated Urethral System for Erection). This product is preferred by some patients to the injection therapy, but the typical side-effects limit its usefulness. These include urethral pain in 25–43% of patients and occasionally urethral bleeding (in 5%).

Vacuum erection devices

Vacuum erection devices are the other main form of treatment for diabetic men with ED, and a number of studies have confirmed their efficacy in such men. Prior to the use of oral agents, one study reported that, when given the choice, 44 of 54 men chose vacuum therapy over injection therapy and that 75% of them were able to achieve a satisfactory erection after 2 months. Another group suggested that vacuum erection devices might provide an effective alternative in the significant proportion of diabetic men who fail to respond to intracorporal injections.

Other treatments

Androgen deficiency has a role in the pathogenesis of ED in patients with diabetes, and while some studies have shown moderate efficacy for testosterone in the treatment of these patients, others have not. However, it is obviously important to diagnose and to treat any remediable endocrinological causes for the ED, particularly in the young diabetic patient. In a number of patients, psychological factors will be important. One group reported the value of initial psychosexual
assessment: in 52% of their patients, significant psychosexual factors were identified and, of 24 men with diabetes who then went on to receive psychosexual therapy, 60% were successfully treated.20

Vascular surgery

Patients with diabetes often have co-existing arteriosclerotic disease and, in some cases, this may be the primary factor in the pathogenesis of the ED. In a few cases, either aorto–iliac reconstruction or angioplasty may theoretically improve the penile circulation; however, this is rarely indicated or effective. Similarly, reconstructive microvascular surgery is also often unsuccessful, even in the hands of enthusiasts. The current consensus is that, in patients with arteriosclerotic disease, arterial–arterial anastomosis is not indicated. Dorsal vein arterialization has been shown to be effective in a proportion.29 The obvious problem with patients with diabetes is that, even if any reconstructive procedure is technically successful, effective erections may not be possible because of co-existing neuropathy or endothelial dysfunction.

Penile prostheses

If all other treatments have failed or have proved unacceptable, the final therapeutic option remaining is a penile prosthesis. The different types of implant, the selection criteria for surgical implantation and the techniques of surgery have all been outlined elsewhere in this volume and apply equally to patients with diabetes. However, where the use of implants in these patients does differ from that in other patient groups is in the septic complications of surgery. Most importantly, it appears that diabetic patients are probably more prone than the general population to infection of the prosthesis. Certainly, a number of early studies all suggested an increased risk of infection in diabetic patients.96–98 A British group confirmed this increased infective risk in a group of patients operated upon between 1985 and 1990. Interestingly, however, they were able to reduce the risk of prosthesis infection significantly by adherence to a meticulous preoperative, intra-operative and postoperative regime. When they used this protocol on a group of 62 patients, there was only one infected prosthesis, and in the 13 diabetic patients there were no infections at all.99

A much larger series has reviewed the results of 1337 implants and has reported no increased risk of prosthesis infection in diabetic patients compared with the general population.100 Prosthesis revision surgery was reported, although this did not reach statistical significance. The difference between the older results and the more recent reports may simply reflect more meticulous preoperative preparation, better antibiotic prophylaxis, and improved surgical technique.

However, when infections do occur in patients with diabetes the consequences can be severe. An early report described three cases of gangrene of the penis following implantation of a prosthesis in patients with insulin-dependent diabetes; in two of the patients, penile amputation was required.101 As to the reasons behind this apparent increased risk of periprosthetic infection, there is controversy as to whether poor control of the diabetes is important. Data suggest that preoperative glycosylated hemoglobin levels in excess of 11.5% predispose to periprosthetic infections,102 whereas another prospective study showed no correlation between the glycosylated hemoglobin and the risk of prosthesis infection: indeed, there were no infected prostheses in the group of patients with poorly controlled diabetes.103

Conclusion

The etiology of ED in diabetes mellitus is multifactorial, with neurovascular and endothelial factors playing a prominent role. There has been much research into the underlying pathophysiology and there is still much to learn. Patients with diabetes will continue to present with ED in increasing numbers owing to the rising prevalence of obesity in our communities. Therefore, we need clear strategies to deal with the problem and reduce the stress and anxiety that accompanies the disease.

REFERENCES

Erectile dysfunction and diabetes


71. Cartledge JJ, Eardley I, Morrison JF. Impairment of corpus cavernosum smooth muscle relaxation by glycosylated human haemoglo


Introduction

Erectile dysfunction (ED) is defined as the persistent inability to attain or maintain penile erection sufficient for sexual intercourse. In men with chronic renal failure (CRF), quality of life is significantly impacted by ED. The etiology is often multifactorial. Uremia, medications, associated comorbid conditions, physiologic changes with dialysis, and the causative pathophysiology leading to the patient’s CRF should all be considered prior to initiating treatment (Table 60.1). Regardless of the primary cause, ED can have a negative impact on self-esteem, quality of life, and interpersonal relationships.

Incidence of erectile dysfunction in chronic renal failure

Abnormalities in male sexual function and reproductive function have been widely reported in patients with CRF. Studies in which patients and spouses were interviewed or evaluated by questionnaire have demonstrated impotence in 20–60% of patients surveyed. Masters and Johnson reported that the incidence of ED in normal men under the age of 50 years was less than 5%. The Massachusetts Male Aging Study reported that 5% of men at age 40 years have complete ED; and this rises to 50% among men aged 70. Rodger et al. reported on 100 uremic men with a significantly higher prevalence. In a more recent study, Rosas et al. found that 82% of patients on hemodialysis had ED. ED was much more prevalent in the dialysis patients older than 50 years (63% in those younger than 50 compared with 90% in those older than 50).

Using nocturnal penile tumescence (NPT) monitors, Karacan et al. observed that rapid eye movement (REM) sleep was associated with penile tumescence. These studies proved that organic disturbances or pharmacological alteration of physiology correlated with altered NPT and impotence. If psychological factors predominate, the NPT results should not be affected. Karacan et al. reported that 50% of patients on hemodialysis had abnormal NPT. Thus, it appears the increased incidence of ED in CRF is not due simply to psychogenic causes. Procci et al. combined questionnaires and NPT monitoring to evaluate further the incidence of ED in uremic males (Figure 60.1). Procci et al.’s results demonstrated a significant abnormality in NPT recordings in 50% of uremic patients on hemodialysis. Questionnaires quantifying frequency of intercourse correlated with NPT findings in this group of patients. Interestingly, the incidence of depression common in uremic patients did not correlate with NPT findings or frequency of intercourse. Thus, this study strongly suggests an organic or physiological cause for ED in uremic patients on hemodialysis.

Chronic renal failure and causes of erectile dysfunction

As a result of the multisystem disease processes present in many uremic men, it is apparent that the pathogenesis of impotence is most probably multifaceted. Uremic men complain of loss of libido, loss of potency, inadequate or lost ejaculation, and decreased penile sensation. Alterations in venous and arterial flow patterns, altered smooth muscle tone, hormonal aberrations, neurogenic abnormalities, and structural damage secondary to infection, trauma, or associated diseases should all be considered in the initial evaluation of physiologic causes of ED. In addition, chronic fatigue, depression, and psychosocial stress may result from chronic, indolent illnesses that can contribute as psychological components of ED (Figure 60.2).

Erectile dysfunction and physiologic changes

The physiologic processes that contribute to erectile problems in patients with CRF include vascular insufficiency and venous incompetence, neurologic compromise, endocrine abnormalities, diminished oxygen delivery, pharmacologic manipulations, psychological disturbances, and associated chronic diseases (such as hypertension, diabetes mellitus, anemia, and electrolyte abnormalities). Often, multiple physiologic abnormalities contribute to the patient’s ED.

Vascular insufficiency

Nitric oxide is released by sexual stimulation. The role of nitric oxide in erectile function has been well defined, and it works to relax smooth muscle and dilate the arterioles, thus increasing blood flow. Blood trapped in the expanding sinusoids compresses the venous system, increasing the pressure within
the cavernosal bodies to approximately 100mmHg. Contraction of the ischiocavernosus muscle further raises pressure in the penis, leading to a rigid erection.

It is well known that patients with uremia or on chronic hemodialysis have accelerated atherosclerosis associated with both large-vessel and small-vessel occlusive disease. Vasculogenic ED from occlusion of large vessels and their arterial tributaries is a result of the acceleration of atherosclerosis. Therefore, vasculogenic ED occurs even in younger men with CRF. Kaufman et al. reported that 78% of impotent CRF patients had significant occlusive disease of the cavernosal artery. The multifactorial nature of vascular insufficiency in uremic patients makes specific treatment difficult. Diabetes mellitus, smoking, hypertension, hyperlipidemia, and multiple medications are all factors producing arterial insufficiency in these patients. Since many dialysis patients require continuous antihypertensive therapy, hypertension and its treatment.
medications can be strongly suspected as contributing to arterial ED. Since as many as 15% of uremic patients are diabetic, diabetic vascular changes also can be expected to contribute to ED.

Additionally, those patients who have undergone renal transplantation may have vascular compromise to their lower extremities and genitalia. These vascular changes can be documented using Doppler sonography and are well reported.16 Techniques to identify venous outflow abnormalities in ED include dynamic infusion studies, pharmacoangiometry, and pharmacocavernosography.17 These studies, combined with color Doppler evaluation of arterial inflow, are necessary to identify specific vascular abnormalities producing ED. In a series by Kaufman et al., 90% of CRF patients had venous occlusive incompetence.15 Veno-occlusive dysfunction as a cause of erectile problems probably results from a combination of venous vascular abnormalities associated with peripheral smooth muscle function of the corpora cavernosa.

Neurogenic alterations

Autonomic control of erectile smooth muscle tissue is critical in the maintenance of erectile function. Sympathetic neural activity predominates in the flaccid state and during detumescence of the erectile bodies. Norepinephrine activates postsynaptic alpha-1a, alpha-1b, and alpha-1c receptors, and its activity is modulated by presynaptic alpha-2 receptors.18 The parasympathetic system mediates erections via acetylcholine. Activation of muscarinic receptors liberates nitric oxide, which relaxes smooth muscle and causes erection. There are also non-adrenergic, non-cholinergic (NANC) neurons that release nitric oxide. Nitric oxide increases cGMP production, which relaxes cavernous smooth muscle.19

Campese et al. studied the autonomic nervous system in uremic patients by monitoring the heart rate response to the Valsalva maneuver.20 This technique can, to some extent, measure the integrity of the afferent parasympathetic and efferent sympathetic pathways. In studies of 12 CRF patients with ED, an abnormal Valsalva maneuver correlated with abnormal NPT and diminished ability to achieve erections suitable for intercourse. These data suggest that autonomic nervous system dysfunction is an etiological factor in impotence associated with uremia.

Peripheral neuropathy in CRF is frequent. Peripheral neuropathy that occurs most commonly in patients with diabetes mellitus also can be seen in patients with non-diabetic uremia. Although there are few satisfactory neurophysiological tests to identify patients with neurogenic impotence, clinical neurophysiology can be useful in assessing patients with defects in somatic nervous system pathways to the sacral segments affected by uremia, diabetes, or other metabolic disease processes. Practitioners must rely on clinical judgement when evaluating patients with suspected neurogenic causes for impotence.20

Psychological factors

The psychological impact of uremia and its treatment and management have a significant role in sexual dysfunction in patients with CRF. Patients with uremia, especially those on hemodialysis, have a significant incidence of psychiatric and depressive illness compared with the normal population.7 These psychological abnormalities will certainly add to the already significant physiological abnormalities in these patients. The psychological conditions identified include low self-esteem; lack of a sense of wellbeing: a significant increase in stress from chronic illness, job loss, and financial concerns; and a documented increase in depression and marital discord. Dunante et al. clearly demonstrated the association between depression, its severity and ED in the Massachusetts Male Aging Study.21 Procci et al. have identified a higher incidence of depressive episodes in patients on hemodialysis in comparison with a normal population.8 Glass et al. studied the psychological impact of CRF, dialysis, and renal transplantation and found that dialysis patients were more likely to be depressed than transplant patients, whereas transplant patients showed a greater level of anxiety.9 Marital discord rates were higher in all patients with CRF, and they were especially marked in those patients on hemodialysis. The findings of Glass et al., which demonstrated impotence in many patients in whom physiological erectile function could be measured, suggested that psychological stresses and abnormalities were a significant part of uremic sexual dysfunction.8

Abnormalities in the endocrine system

The kidney plays an integral role in endocrine function. Hormonal effects of the kidney are well known, and the kidney provides significant hormonal metabolism. CRF, therefore, can be expected to produce profound changes in endocrine function and hormone balance that affect many bodily functions, including male sexual activity.

The hypothalamic–pituitary–gonadal axis is negatively affected by CRF; this has been well documented (Figure 60.3).22–25 Decreased testosterone levels are common, and this correlates with inferior semen quality.23 These abnormalities are supported by testicular histological abnormalities on biopsy, including abnormalities in both spermatogenesis and interstitial cell morphology.26

Most male patients with CRF on dialysis have low serum testosterone levels, although many may be at the low end of the normal range.26 Low testosterone levels are most probably caused by decreased testosterone production, but there is evidence for elevated metabolic clearance of testosterone in addition to decreased production.22,24,26 As a result of normal testicular binding capacity, free testosterone and salivary testosterone levels are low.2,23,24,26 These abnormalities have been identified in patients despite differing methods of dialysis including hemodialysis and peritoneal dialysis (continuous ambulatory peritoneal dialysis, CAPD).29,30 Some dialysis patients have elevated levels of testosterone-binding globulin, and some patients have normal testosterone and free testosterone levels.31–33 The levels of free and total testosterone remain low despite attempted stimulation with administration of exogenous human chorionic gonadotropin.34 Thus patients with CRF are likely to have a deficiency in hormone production and secretion as the primary mechanism for their hypogonadism, as well as an element of end-organ failure.

Investigation of patients immediately after initiation of dialysis in early uremia demonstrates an initial elevation
production is quite normal. The rise in serum LH and FSH correlates well with the pituitary response to hypothalamic stimulation by GnRH, which is preserved in the CRF patient. Thus, if the LH response to low testosterone levels is inadequate, a pituitary abnormality may be present.

Sexual dysfunction may be due to the frequently elevated prolactin levels in men with CRF. Sexual dysfunction is commonly experienced by patients with normal renal function and hyperprolactinemia caused by pituitary neoplasms or pharmacological abnormalities. Although the mechanism of sexual dysfunction caused by hyperprolactinemia remains controversial, loss of libido, decreased erectile function, and infertility have been widely associated with elevations in prolactin. The cause of sexual dysfunction in those patients with elevated prolactin may be a disordered hypothalamic–pituitary axis or a direct peripheral gonadal effect of prolactin. Hyperprolactinemia without renal failure usually results in increased levels of LH and hypogonadism. This response differs from the usual low testosterone and low LH associated with the hyperprolactinemia of CRF. Hyperprolactinemia can be induced by several medications, including methyldopa, digoxin, cimetidine, and metoclopramide. Patients with hyperprolactinemia often have ED. Once the hyperprolactinemia is treated, erectile function improves, as does fertility.

Other endocrinologic abnormalities can strongly contribute to ED in patients with CRF on dialysis treatment. Most common among these is diabetes mellitus, which is one of the most common causes of ED. Vascular changes in long-term insulin-dependent diabetic patients are well known and cause corporal arterial insufficiency and veno-occlusive dysfunction. The autonomic and sensory neuropathic dysfunctions resulting in ED are not amenable to medical therapy. This is especially difficult for the young patient who has adequate vascular and venous function but insufficient neurologic ability to produce a sufficient erectile response.

Other hormonal abnormalities that contribute to ED in uremic men include abnormalities in parathyroid hormone (PTH). Secondary hyperparathyroidism is a common manifestation of CRF. Massry et al. suggested in 1977 that the excess blood levels of PTH in uremic patients might contribute, at least partly, to the disturbance in hormones of the hypothalamic–pituitary–gonadal axis and in the genesis of the impotence of uremia. They reported on two impotent dialysis patients in whom sexual function was restored following parathyroidectomy without other changes in CRF management.

Anemia and diminished oxygen delivery

Hypoxia associated with CRF has been implicated as a potential cause of ED. Two sources of hypoxia in CRF have been identified — pulmonary-associated hypoxia and anemia-associated hypoxia. Pulmonary-associated hypoxia is due to hypoventilation and pulmonary microembolization, whereas anemia-associated hypoxia is due to diminished erythropoietin production. Hypoxia can lead to ED by affecting nitric oxide synthesis in the corpora cavernosa. Cavernosal nitric oxide synthesis is impaired by low partial pressures of oxygen. The decreased nitric oxide synthesis subsequently leads to worsened erectile function in patients with CRF.

Men with CRF have abnormal secretion of luteinizing hormone (LH), follicle-stimulating hormone (FS), and prolactin. LH levels are generally increased in response to low testosterone levels and because of a decrease in the metabolic clearance of LH. It has been estimated that LH levels exceed 20% of normal in many of these patients, probably as a result of decreased testosterone levels caused by hypogonadism. FSH is also elevated in those men with suboptimal spermatogenesis. Holdsworth et al. have suggested that the FSH levels in patients with uremia can be used as prognostic indicators for the return of fertility following renal transplantation. Occasionally, pituitary abnormalities can be suggested by low LH levels despite low testosterone concentration; more commonly, however, pituitary response to gonadotropin-releasing hormone (GnRH) with increased FSH and LH

Figure 60.3 Behavior of serum hormone in males during the 18-month follow-up. *p<0.05; **p<0.001 vs basal. Reproduced with permission from Contrib Nephrol 1990; 77: 34–44.
found decreased nitric oxide synthesis and elevated smooth muscle tone in patients with low oxygen tension at the corpora cavernosa. Luscher et al. found increased endothelium-derived contracting factors, which could further increase smooth muscle tone and inhibit erection. Finally, metabolites that inhibit nitric oxide synthase accumulation in CRF patients may possibly contribute to the ED.

Pharmacological factors

Because of the underlying conditions that have produced ED in patients with CRF, close attention must be paid to erectile abnormalities associated with medications. Pharmacological treatment of conditions associated with CRF may produce side-effects causing or increasing impotence and diminished libido. Table 60.2 lists the medications frequently associated with ED. Such agents may produce abnormalities in central, neuroendocrine regulation or in the neurovascular control of erectile function, either in the corpora cavernosa or at a central level. Centrally acting agents like clonidine and reserpine, as well as drugs that increase prolactin levels, frequently result in decreased libido.

ED has been associated with virtually all antihypertensive agents. These antihypertensive medications, added to the associated physiological arterial changes noted to occur with atherosclerosis, magnify the problem of ED in these patients. Calcium-channel blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and alpha-adrenergic antagonists are least likely to cause iatrogenic ED.

On the other hand, beta-blockers, sympatholytics, and vasodilators are strongly associated with local effects that overcome the normal physiological response of the smooth muscles of the corpora cavernosa and (locally as well as centrally) inhibit erectile function. These drugs, if causing ED, may be changed to alpha-adrenergic blocking agents such as terazosin, prazosin, or doxazosin, or ACE inhibitors and calcium-channel blockers. Many dialysis patients are treated with sympatholytic medications such as methylpap and clonidine, beta-blockers such as propranolol, and vasodilators such as hydralazine. Patients treated with these agents can be expected to exhibit physiological ED as a result of the local cavernosal effects of these agents. Alpha-2 adrenergic antagonists, such as clonidine, may produce central cavernosal artery constriction or limit its dilatation potential, decreasing cavernosal perfusion and diminishing erectile function.

Evaluation of erectile dysfunction in men with CRF

It is clear from the foregoing discussion that the causes of ED and infertility in uremic men can be multifactorial. ED in men with CRF should proceed systematically (Table 60.3) and

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<th>Table 60.2</th>
<th>Pharmacological agents frequently used in chronic renal failure and associated with sexual dysfunction</th>
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| **Antihypertensive agents** | Sympatholytics  
Methyldopa  
Clonidine  
Reserpine  
Guanethidine |
| **Beta-adrenergic antagonists** | Propranolol  
Pindolol  
Atenolol  
Metoprolol  
Labetalol |
| **Vasodilators** | Hydralazine |
| **Diuretics** | Thiazides  
Spironolactone |
| **Antidepressants** | Tricyclics  
Serotonin reuptake inhibitors |
| **Other agents** | Cimetidine  
Digoxin  
Clofibrate  
Metoclopramide |

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<th>Table 60.3</th>
<th>Evaluation of erectile dysfunction in men with chronic renal failure</th>
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| **History** | Physical examination  
General examination  
Genitourinary examination: testicles, scrotum, phallus, meatus, prepuce, and glans  
Digital rectal examination  
Neurological examination: S2–S4 sensation, bulbocavernous reflex, anal wink, anal tone, and penoscrotal sensation |
| **Laboratory evaluation to assess general and specific causes of erectile dysfunction** | Serum testosterone  
Luteinizing hormone  
Follicle stimulating hormone  
Prolactin  
Complete blood count  
Serum glucose or glycosylated hemoglobin and baseline electrolytes  
Lipid profile  
White men >50 years and black men >40 years should have a prostate-specific antigen test |
| **Further referral to a urologist if considering certain studies** | Doppler screening studies  
Color Doppler ultrasound for flow  
Pharmacocavernosography  
Pharmacocavernosometry  
Dynamic infusion studies  
Nocturnal penile tumescence studies  
Biothesiometry  
Injection therapy  
Surgical therapy |
always begin with a thorough history and physical examination. A careful history to identify psychological factors, such as significant depression, must be carried out by a qualified mental healthcare professional. A careful physical examination, including studies for the identification of peripheral neuropathy and vascular abnormalities, is also helpful. The use of NPT monitors can identify patients with a true organic cause for their ED in whom vascular problems are suspected. In patients in whom veno-occlusive incompetence or arterial abnormalities are suspected by Doppler screening studies, pharmacocavernosometry, pharmacocavernosography, and dynamic infusion studies, together with color Doppler arterial response studies, may be helpful, especially if a surgical intervention is planned.

Finally, hormonal studies, including testosterone, LH, FSH, and prolactin, should be obtained. These may be supplemented by serum glucose, glycosylated hemoglobin, lipid profile, and thyroid function studies. Communication with the nephrologist and transplant surgeon is essential, since transplantation may reverse many of the previously mentioned abnormalities of uremia, and initiation of specific impotence treatment modalities may be delayed until after transplantation is carried out in some patients.

### Treatment options

Treatment options for ED are reviewed in Table 60.4.

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<td>Adjust medications where appropriate</td>
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<td>Evaluate for psychosocial stresses</td>
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<td>Discuss expectations with patient</td>
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<td>Routinely evaluate efficacy of therapy and patient satisfaction</td>
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<tr>
<td>Realize the changing patterns of erectile dysfunction and need to change therapy or modality</td>
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<td>Consider early referral to a urologist</td>
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### Medical management

**Hormone regulation**

Patients who have low testosterone levels may respond to replacement therapy, which normally improves libido without a significant impact on potency or fertility. Data on the effects of testosterone replacement in end-stage renal disease are scant. There have been several small studies suggesting that testosterone therapy does not improve erectile function in the majority of hemodialysis patients for whom it was prescribed.54–56 Effective replacements include injectable preparations, transdermal delivery systems, or sustained-release products. However, testosterone 100–200mg weekly by injection produces only small and variable responses in erectile function.57

Clomiphene citrate, which is a partial agonist of the estrogen receptor, increases secretion of gonadotropins and increases plasma testosterone in CRF. One study used clomiphene citrate to increase testosterone levels from the hypogonadal range to the high end of the normal range in five uremic men. The five men subsequently reported uniform increases in libido and sexual function.58

If hyperprolactinemia is found, chromophobic tumors of the anterior pituitary must be excluded, since these may present with ED or decreased libido. Pharmacological methods for decreasing hyperprolactinemia also appear to be effective in some men with uremia-associated sexual dysfunction. Methyldopa and reserpine interfere with dopamine secretion and therefore lead to hyperprolactinemia. If these causes are excluded, dopaminergic agonists may be of benefit.59

Bromocriptine (1.25–5mg daily) and lisuride hydrogen maleate (0.05–0.2mg daily) decrease prolactin and elevate testosterone. Bromocriptine can induce hypotension, nausea, vertigo, and dizziness – side-effects that are intolerable to many patients. These side-effects are less prominent with lisuride hydrogen maleate. Subsequent rises in plasma testosterone, with expected improvement in sexual function, result from these medications.

For patients with symptomatic secondary hyperparathyroidism, it was recently found that sexual function of male patients can be improved by parathyroidecotomy and autotransplantation. The report also demonstrated a decrease in the levels of prolactin in association with decreasing levels of calcium, phosphorus, and immunoreactive PTH.49

CRF and uremia are frequently associated with profound anemia, which may result in psychological ED caused by weakness, fatigue, and anxiety. The physiological effects of anemia and hypoxia on erectile function have been described previously in this chapter. Treatment of anemia with recombinant human erythropoietin in male uremic patients has been reported to improve sexual performance and fertility and to increase serum testosterone and FSH levels. Although the studies on recombinant human erythropoietin are preliminary, there appears to be some salutary effect of this method of treatment in some uremic patients.55,63

**Phosphodiesterase type 5 inhibitors**

Since 1998 the Food and Drug Administration in the USA has approved three selective phosphodiesterase (PDE) type 5 inhibitors: sildenafil, tadalafil, and vardenafil. Each of the
registration programs of the PDE-5 inhibitors involved more than 2000 patients. In the USA, sildenafil was approved in 1998 and both vardenafil and tadalafil were approved in 2003.

Erectile function depends on the neuronal pathways (NANC neurons) and release of nitric oxide.\(^{53,64}\) PDE-5 inhibitors inhibit the breakdown of cGMP, thereby allowing continued relaxation of smooth muscle in the corpus cavernosum.\(^{65}\) All three drugs in this class have similar pharmacokinetic and pharmacodynamic profiles, and each is effective for patients with ED in all ages and of all severities and etiologies.

In patients with CRF, sildenafil has the longest patient experience and the most robust data confirming its activity, safety, and tolerability. The best results in the initial human trials were obtained with sildenafil 100mg; however, up to 24% of men responded effectively on the 50mg dosage schedule. Also significant was the increase in frequency of intercourse, with those receiving sildenafil making on average 5.9 successful attempts per month compared with 1.5 among those receiving placebo.\(^{66}\) Sildenafil studies in patients on dialysis show a good response rate (66.7–80%). The majority of sildenafil responders had success with the 50mg tablets.\(^{67,68}\) Sildenafil has been shown to be effective in patients with difficult-to-treat ED, and the Sildenafil Diabetes Study Group showed that 56% of men with ED and diabetes who received sildenafil (25–100mg) for 12 weeks reported improved erections, in contrast to 10% of patients receiving placebo (p < 0.001).\(^{69}\)

Sildenafil given to transplant patients does not affect levels of anti-rejection medications and has a 60% satisfactory response rate.\(^{70}\) Most commonly reported side-effects are headache (16%), flushing (10%), and dyspepsia (7%).\(^{71}\) Concomitant nitrate administration can lead to hypotensive side-effects in some patients. It is unclear how long the patient must wait until nitrates can be safely administered. Sildenafil decreases systolic and diastolic blood pressure by 10mmHg and 7mmHg, respectively. Nitrate use leads to a synergistic increase in cGMP levels, which can cause excessive hypotension and occasionally ischemic cardiac events or strokes.\(^{72}\) Sildenafil can be safely administered in CRF if there is no serious cardiac disease. Sildenafil is primarily metabolized in the liver but there is some renal excretion; lower doses (25mg) are recommended initially in CRF patients.

In vitro studies have shown that the potency of vardenafil in inhibiting PDE-5 purified from the human corpus cavernosum tissue was approximately 25 times greater than that of sildenafil and 48 times greater than that of tadalafil.\(^{73}\) In a study by Hellstrom et al., many patients returned to normal erectile function after treatment with vardenafil.\(^{74}\) For example, 89% of patients with mild ED at baseline returned to normal function after treatment with vardenafil 10mg. Forty percent of patients with severe ED at baseline returned to normal function after treatment with vardenafil 20mg, compared with only 4% who received placebo. There is limited evidence that a small percentage of sildenafil non-responders can be salvaged with vardenafil.\(^{75}\) A starting dose of 5mg of vardenafil should be used in men with severe renal impairment.\(^{76}\)

Recent double-blind, placebo-controlled, multicenter trials have assessed the efficacy and safety of tadalafil in the treatment of ED. Significant improvements from baseline in the erectile function domain score of the International Index of Erectile Function, successful penetration attempts and successful intercourse attempts, and overall satisfaction compared with placebo have reported with an on-demand schedule of the drug.\(^{77,78}\) Tadalafil has a terminal half-life of 17.5 hours, which is consistent with a broad window of clinical responsiveness.\(^{79,80}\) Tadalafil enhances erectile function in men with ED for up to 36 hours. Thus, tadalafil may be associated with less planning or pressure to have sexual intercourse after dosing. Unlike sildenafil and vardenafil, meal intake has no effect on the absorption of tadalafil.

The cytochrome P450 system is the chief metabolic pathway for sildenafil, vardenafil, and tadalafil. All three agents are P3A4 substrates, and concomitant administration with P3A4 inhibitors such as ritonavir, indinavir, ketoconazole, and erythromycin can increase plasma levels of the PDE-5 inhibitors.\(^{81,82}\) Because PDE-5 inhibitors potentiate the vasodilator and hypotensive effects of nitric oxide, treatment with any PDE-5 inhibitor is contraindicated in patients taking organic nitrates.\(^{81,83}\) According to USA prescribing information, co-administration of alpha-blockers with sildenafil, vardenafil, and tadalafil is listed as a precaution.\(^{81,83}\) None of the three agents is dangerously associated with prolongation of the corrected QT interval.

The recent advent of vardenafil, which has the highest in vitro potency of all available PDE-5 inhibitors, and of tadalafil, which has a prolonged half-life that may enable couples to have sexual activity with less planning, represent further advances. However, while there are clear pharmacokinetic differences amongst these agents, the data from preference trials, head-to-head clinical trials, and selection trials are few.\(^{84}\)

Intracavernosal injection therapy

Alprostadil, an exogenous form of prostaglandin E (PGE)-1, is administered by intracavernosal injection. Alprostadil causes smooth muscle relaxation, vasodilatation, and inhibition of platelet aggregation. Some 96% of alprostadil is locally metabolized within 60 minutes. No change in peripheral blood levels occurs, because of extensive pulmonary metabolism.\(^{85}\) Linet and Neff concluded that alprostadil produced full erections in 70–80% of patients.\(^{86}\) Side-effects include pain (17%), hematoma or ecchymosis (1.5%), and priapism or prolonged erection (1.3%).\(^{86}\)

Other agents used alone or in combination with PGE-1 include papaverine and phentolamine mesylate. Papaverine inhibits PDE, leading to increases in cAMP, elevated nitric oxide, and eventual relaxation of cavernosal smooth muscle and arterial dilatation. Kapoor et al. reported on the use of papaverine in men with spinal cord injuries, of whom 98% obtained satisfactory erections capable of successful penetration.\(^{87}\) Papaverine, however, causes priapism and fibrosis in up to 35% and 33% of men, respectively, with increased incidence in young and neurogenic ED patients.\(^{88}\)

Phentolamine mesylate is a competitive non-selective alpha-adrenergic receptor antagonist. It has been used in combination with papaverine to increase blood flow. Side-effects include hypotension, reflex tachycardia, and nasal congestion.

These agents can be used successfully in CRF patients with vascular compromise, diabetic microangiopathy, moderate...
atherosclerosis, and partial arterial dysphasia, although higher doses may be necessary. Patients with veno-occlusive disease may also benefit from increased engorgement of the corpora, leading to increased compression of the tunic albuginea and, therefore, occlusion of the emissary veins. It is interesting to note that patients with neurogenic and hormonal causes of ED also do well with this therapy (as do older patients), without increased side-effects. Long-term use of these injection therapies is effective, with few complications in transplant patients.\(^9\) No major complications on transplanted kidneys have been noted. Contraindications to therapy include sickle cell anemia, severe psychiatric disorders, severe venous incompetence, and severe systemic disease.

Transurethral suppositories

The transurethral delivery system marketed as the Medicated Urethral System for Erection (MUSE), allows for delivery of alprostadil to the corpora by direct venous communication.\(^9\) The mechanism of action of alprostadil has been discussed earlier. Although the system has not been tested in patients with CRF, it has been effective in the treatment of ED arising from most other causes.

**Devices**

Vacuum constriction devices work by engorging the penis with blood by negative pressure. A constriction band is placed at the base of the penis, through for no longer than 30 minutes in order to avoid injury. These devices have local side-effects such as pain from the constriction band, entrapment of ejaculation by the constriction band, a cold and dusky penis, numbness of the penis, and local irritation. Many men use these devices. Using the device can be difficult for men with a short penis or an extensive suprapubic fat pad. In those who need pharmacological manipulation for an adequate erection but who have evidence of venous incompetence, a constriction band alone may be used to sustain rigidity of the penis that is suitable for intercourse.

**Surgical treatment**

Vascular procedures for erectile dysfunction

As most patients with renal failure have small-vessel disease, the use of revascularization techniques and veno-occlusive surgery is not commonly employed. In selected patients, however, balloon dilatation of pelvic arteries may be helpful, with low morbidity expected.\(^9\)

Penile prostheses

Implantation of a penile prosthesis is safe and usually successful, with low morbidity. Renal transplant patients commonly benefit from the device.\(^9\) Such procedures should be performed after renal transplantation, if possible, because many men have improved sexual function, fertility, and potency after the operation. In immunocompromised patients, the risks of implanting an artificial device include prosthetic infection.\(^9\) Cuellar et al. examined their own cohort of 46 patients who had undergone pelvic organ transplant prior to placement of a penile prosthesis.\(^9\) The risk of infection after insertion of penile prostheses in patients with pelvic organ transplantation was similar to that in non-transplant patients.

**Renal transplantation**

As a result of normalization of metabolic and hormonal function in patients after successful renal transplantation, many patients report improved erectile function and libido following heterotopic renal transplantation. Testosterone levels return to normal within 2–3 months, as do LH, FSH, and prolactin levels. Sperm counts normalize in 9–16 months.\(^9\) Patients who receive human chorionic gonadotropin stimulation show improved responses, with higher testosterone levels. Salvatierra et al. found pre-transplant potency to be 22\% while on dialysis; however, after renal transplant, 84\% of men resumed levels of potency comparable to a time before the onset of uremia.\(^9\) Post-transplant psychological disturbances, except for anxiety, appear to diminish.

Although data are limited, studies evaluating commonly used immunosuppressive agents such as cyclosporine, azathioprine, tacrolimus, and prednisone suggest that these agents do not have significant effects on the sex hormone profiles of renal transplant patients.\(^9\) Sirolimus, a new immunosuppressive, has been found to lower total testosterone and increase LH and FSH in renal transplant patients; however, this has not proven to result in a change in sexual function.\(^9\)

It is important to remember that a significant proportion of post-transplant men will continue to have ED despite normalization of hormone values and improved physiology.\(^9\) Causes of post-transplant impotence include failure to resolve hormonal abnormalities, underlying disease processes that have resulted in continued ED, and the effects of the transplant itself. Many of these patients suffer from vasculogenic ED. Reports of marked increase in ED following bilateral renal transplantation may be a result of changes in pelvic hemodynamics resulting in decreased penile blood flow, although reports of patients who are potent following interruption of bilateral hypogastric arteries are common. Impotence following sequential bilateral renal transplantation, however, appears to be increased as a result of decreased blood flow associated with the ligation of both internal iliac arteries. These patients should be evaluated in a way similar to pre-transplant patients, and treatment plans should be generated for their specific needs.

**Conclusion**

Sexual dysfunction is common in patients with CRF. Sexual dysfunction in these patients should be thought of as a multifactorial problem that is affected by a variety of physiological and psychological factors, as well as by comorbid conditions. ED includes a vast array of organic, anatomic, and psychosocial elements, which make evaluation and treatment complex. However, a practitioner who takes a good history and performs a good physical examination and laboratory evaluation can provide a great service to the quality of life of the patient.
with CRF. The physician must address the topic and make the patient feel comfortable with his changing physiology and anatomy. Renal transplantation has the potential to normalize hormone profiles and subdue some of the physiologic changes, although it may not solve the problem because of associated comorbid conditions. Psychological, medical, and surgical therapies can be highly effective in correctly evaluated patients. A multidisciplinary approach to care should be employed, involving the primary care physician, a nephrologist, a urologist, a psychiatrist, and a psychologist.

REFERENCES

Evaluation of ejaculatory disorders

Jason M Greenfield and Craig F Donatucci

Introduction

Ejaculatory dysfunction, especially premature ejaculation (PE), is one of the most common sexual complaints of adult men. The National Health and Social Life Survey (NHSLS) conducted in the USA in 1992, examined sexual complaints in a cohort of over 1200 men. The results of this survey revealed an incidence of PE of approximately 30%, while 7–9% experienced anorgasmia. Ejaculatory disorders as a whole are quite prevalent in patients with benign prostatic hyperplasia (BPH) and lower urinary tract symptoms (LUTS). Clinical studies have estimated the incidence of these disorders to be approximately 30–80% and that they increase as men age.2,3

Although once thought to be purely psychological conditions, ejaculatory disorders are also influenced by organic factors and have recently begun to receive greater interest. Certainly, this may be partially attributed to the greater overall attention paid to sexual dysfunction in men that has accompanied advances in treatment options for men with erectile dysfunction (ED). Although the guidelines of diagnosis and management of ED are still in evolution, a standardized approach to the patient with a disorder of ejaculation is even further behind.

This chapter serves to outline and distinguish the various ejaculatory disorders as well as provide information regarding the approach to their diagnosis and initial management. The bulk of this chapter focuses on premature ejaculation, owing to a recent surge in research and development of knowledge about this particular disorder.

Overview of ejaculation

Ejaculation is composed of two separate events, emission and ejaculation. Before this process is initiated, the bladder neck closes. During the emission phase, sperm and seminal fluid are deposited into the prostatic urethra. The ejaculation phase specifically consists of the muscular contractions and subsequent expulsion of contents from the urethra, normally out the urethral meatus.4 Although orgasm is commonly associated with ejaculation, it is actually a distinct, separate event that occurs centrally.

Emission is mediated by sympathetic fibers (T10–L2) that travel to the pelvic plexus via the hypogastric nerves. Stimulation causes closure of the bladder neck and sequential contraction of the epididymis, vas deferens, seminal vesicles, and prostate, which result in the deposition of sperm and seminal fluid. Ejaculation is mediated by somatic fibers from the sacral spinal cord (S2–S4) via the pudendal nerve, which innervates the bulbospongiosus and bulbocavernous muscles.5

Ejaculation is a reflex involving sensory receptors of the glans penis, afferent pathways (dorsal nerve of the penis), cerebral sensory and motor centers, spinal motor centers, and efferent pathways. Although the exact process is not completely understood, copulatory behavior is regulated by forebrain structures, including the medial preoptic area as well as the paraventricular nucleus of the hypothalamus.6 Studies of the male rat have demonstrated that the neurotransmitters dopamine and serotonin play a major role in ejaculation. While dopamine has been shown to play an excitatory role, serotonin is inhibitory.6,7 Increasing understanding of the role of these neurotransmitters has led to developments in the treatment of ejaculatory disorders over the past few years.

Premature ejaculation

Definition

Premature ejaculation is by far the most common ejaculatory disorder, with rates among US men believed to be as high as 30%, or even greater.1,6 Despite the prevalence of this disorder, PE remains undiagnosed or misdiagnosed in many cases. There are several potential reasons for this. Patients may have embarrassment over their condition, believe the problem is only temporary, or be unaware that PE is a medical problem for which available treatments exist.8 Many physicians also fail to inquire about PE and other sexual disorders. Reasons for this may include lack of time, concern for other medical conditions felt to be more important, embarrassment over asking a patient about sexual dysfunction, or a lack of knowledge or training in sexual disorders.9

One of the initial barriers to the diagnosis of PE has been lack of a consensus on how to define the condition. According to the American Urological Association (AUA) Guidelines, PE is defined as ‘ejaculation that occurs sooner than desired, either before or shortly after penetration, causing distress to either or both partners’.10 It should be noted that in this particular definition there is no mention of a specific time frame in which ejaculation must occur.

The panel for these guidelines also constructed several recommendations for the diagnosis and management of PE. In terms of diagnosis, the panel concluded that the diagnosis of PE is based on sexual history alone, and a detailed sexual history should be obtained from all patients with ejaculatory complaints.11
In 2003 the second International Consultation on Sexual Dysfunctions (ICSD) convened. The definition used by the ICSD for PE is “ejaculation with minimal stimulation and earlier than desired, before or soon after penetration, which causes bother or distress and over which the sufferer has little or no voluntary control.” This panel of experts further proposed that PE is based on three essential criteria:\(^\text{12}\)

1. Brief ejaculatory latency
2. Loss of control over ejaculation
3. Psychological distress to the patient and/or partner.

Further definitions have been proposed citing specific ejaculatory latency times, number of penile thrusts, or responsiveness of the partner, but these have been proven to be unreliable and difficult to support.\(^\text{13}\)

**Etiology**

There is no consensus on the exact etiology of PE and, in fact, it is likely a multifactorial disorder. Many theories have been proposed ranging from psychogenic (e.g., anxiety, frequency of intercourse, evolutionary) to biological (e.g., penile hypersensitivity, hyper-excitability of the ejaculatory reflex, endocrinopathy, serotonin receptor dysfunction).\(^\text{13,14}\) PE has been sub-categorized as either lifelong or acquired. The disorder may also present as situational (occurring only with certain partners or under certain conditions) or global (always occurs during sexual intercourse). It is generally believed that acquired or situational PE is more likely to be due to a psychogenic cause and may be best treated with behavioral therapy whereas lifelong or global PE suggests a biological cause and may be best approached with pharmacologic treatment.\(^\text{13}\)

**History**

A detailed history and physical examination are essential components of the evaluation of the patient with PE (Table 61.1). The clinician should attempt to determine whether the complaint is lifelong or acquired, global or situational.\(^\text{15}\) The ICSD has recommended that the medical history should include assessment of potential comorbid factors including anxiety, interpersonal relationship factors, and other sexual dysfunctions (especially ED).\(^\text{15}\) Based on the panel’s definition of PE, the clinician should also verify the patient’s own subjective assessment of ejaculatory latency, sense of control over ejaculation, and level of distress for him and his partner.\(^\text{13}\) Similarly, the AUA guideline proposed information that should be gathered during the history. Clinicians should determine the onset, frequency, and duration of PE, including the proportion of sexual attempts that are affected by PE. Again, an emphasis is placed on determining whether the PE was lifelong or acquired, situational or global. The frequency and nature of the patient’s sexual practices (masturbation, foreplay, intercourse, etc.) may provide insight. The effect of PE on relationships, sexual activity, and quality of life for both partners should also be a focus of the patient interview.\(^\text{11}\)

An emphasis has been placed on the relationship between PE and ED. In fact, these two disorders have been found to occur together in as high as 30% of patients.\(^\text{16}\) Confusion between these two disorders may arise because PE may be misdiagnosed as ED. Generally, men with ED lose their erection before ejaculation, although the patient or clinician may confuse the actual circumstances. In addition, it is believed that men with ED may actually condition themselves to ejaculate rapidly so that they may complete the act before losing an erection.\(^\text{16}\) This is believed to be PE secondary to ED rather than primary PE. Thus, the AUA guideline currently recommends that patients with both disorders be treated for the ED before PE.\(^\text{16}\) Finally, some men believe the loss of erection following ejaculation to be related to PE although this process is normal. Given these opportunities for misdiagnosis, it is imperative for the clinician to determine whether or not the patient actually ejaculates during intercourse and whether or not ejaculation precedes detumescence.\(^\text{10}\) This gives further evidence to the value of an accurate, detailed sexual history.

A general medical history and physical examination may be necessary, although it is usually less contributory than the sexual history. It may help to rule out any other medical condition or surgical injury that could have an effect on sexual functioning.\(^\text{17}\) During the medical history, attention should be paid toward use of prescription and recreational drugs. Withdrawal from trilafuoperazine, opiates, and ephedrine has been associated with PE or rapid ejaculation.\(^\text{2}\)

**Further evaluation**

Lack of standardized objective criteria for assessing PE has led to difficulty in defining PE and assessing efficacy of treatment. Several criteria have been proposed, including intravaginal ejaculatory latency time (IELT) and number of penile thrusts.\(^\text{16}\) Generally, IELT has been the favored criterion. IELT is defined as the time from the start of vaginal intromission to the time of intravaginal ejaculation. Generally, men with PE have a shortened IELT, which may range from a few seconds to a few minutes. Alternatively, men with PE may actually ejaculate before intromission and therefore have no measurable IELT.

As previously mentioned, no standardized ‘cut-off’ for IELT exists for defining PE. In a recent international study, men who did not report having symptoms of PE were found to have an IELT ranging from 7 minutes to over 13 minutes.\(^\text{17}\) Another international study reported a median IELT of 5.4 minutes and a mean IELT of 8.1 minutes.\(^\text{18}\) Patients and their respective partners have been found to have disparaging opinions on what was the patient’s estimated IELT and

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<td>Frequency and nature of sexual practices (e.g. masturbation, foreplay, intercourse)</td>
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what should be considered ‘normal’. Studies concerning PE using IELT as an instrument of evaluation have measured latency time both as a subjective estimation as well as with a stopwatch.

Owing to the wide variability in reported methodology and findings of ‘normal’ and ‘abnormal’ IELT across studies, the data have been difficult to assess. An observational study conducted in the USA found a mean IELT of less than 3 minutes for men with PE and over 9 minutes for ‘normal’ men. However, there was considerable overlap between each group. Clearly, IELT itself cannot be utilized as a single criterion for the diagnosis of PE. In a recent study, Vanden Broucke et al. sought to determine the normal range and repeatability of IELT in a laboratory compared with at home (masturbation and intercourse), the threshold and repeatability of penile sensitivity on six penile surface areas, and finally whether penile sensitivity correlates with ejaculatory latency time. In a study of 58 healthy men, ejaculatory latency time was found to be highest during intercourse (median 8.25 minutes), lower in the laboratory (7.22 minutes), and lowest for masturbation (4.89 minutes). There was high variability between subjects but scores were reliably reproducible by individual subjects. Reproducible penile sensitivity thresholds were also achieved using two vibrostimulation devices. Interestingly, no correlation was found between penile sensitivity and ejaculatory latency.

More investigation is needed to determine the exact role of measurements of IELT and whether it will become a useful clinical tool in the diagnosis and management of PE. Currently, measurement of IELT is generally reserved for clinical trials and research, and it is not recommended for the routine evaluation of the patient with complaints of PE.

In attempting to define parameters to help to distinguish men with and without PE, an observational study by Patrick et al. identified three measures. These patient-reported outcomes (PRO) were control over ejaculation, satisfaction with intercourse, and distress. Not surprisingly, IELT was found to correlate most reliably with control over ejaculation. Combining IELT and these three core PROs is a potential tool for diagnosing PE and evaluating treatment efficacy. Development of a validated questionnaire to screen for PE has been recently proposed. This may eventually help to combat the lack of an effective screening tool for PE, a major barrier to the diagnosis of this condition.

Summary
Premature ejaculation is a common condition in men that often goes undiagnosed or misdiagnosed. A thorough sexual and medical history is essential to the evaluation. While PE often occurs with ED or may confound the diagnosis, a properly completed sexual history aids in the diagnosis. Measurement of IELT aids in the evaluation of PE but is not reliable as a sole criterion for diagnosis. The diagnosis of PE is based on a brief ejaculatory latency, loss of control over ejaculation, and psychological distress to patient or partner (or both).

Delayed or inhibited ejaculation
Delayed ejaculation (DE) is considerably rarer than PE. In a review of the medical literature, Spector and Casey found inhibited ejaculation to account for 3–8% of patients who present to a physician with a sexual complaint. Although relatively rare, it can be quite distressing to patient and partner. While causing distress to the patient it may also cause the patient’s partner to feel less attractive, undesirable, and sexually inadequate. This may lead to a lack of desire for sexual interaction and stress on the relationship.

Delayed or inhibited ejaculation is defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) as the persistent or recurring difficulty, delay in, or absence of attaining orgasm following sufficient sexual stimulation which causes personal distress. However, the symptom of DE should be differentiated from inhibited orgasm or anorgasmia. Although ejaculation and orgasm commonly occur concomitantly, they are two separate processes and confusion over the diagnosis can result from a lack of a proper patient history.

As with the patient complaining of PE, a detailed sexual and medical history is essential in the evaluation of DE. Again, the clinician should assess whether the patient’s symptoms are lifelong or acquired, global or situational. It may be beneficial to enquire about the patient’s personal and religious views regarding sexual behavior, since this may play a role in DE. As would be expected, the status and quality of the patient’s interpersonal relationship (or relationships) may also have an influence. Men presenting with DE may commonly also admit to relationship stress, fear of inadequate performance, or poor partner arousal.

Other factors to consider include frequency of intercourse and masturbation. Certain habits in masturbation practices have also been proposed to play a role. For example, a man who aggressively masturbates may ‘train’ himself so that he no longer responds to the stimulation experienced with sexual intercourse. Results of the Massachusetts Male Aging Study (MMAS) demonstrated that the incidence of DE increases as men age. Beginning in the third decade of life, progressive loss of peripheral sensory axons occurs. As men age, dermal atrophy, myelin collagen infiltration, and Pacinian corpuscle degeneration occur, and this may lead to progressive penile hypoesthesia.

Several pharmacologic agents have been associated with DE, including serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, methylpopa, monoamine oxidase inhibitors, and certain antipsychotics. Alcohol use or abuse has also been linked to DE.

Identifying the factors that may be causing DE in the individual patient is critical. In order to identify the most effective manner of treating the patient affected by DE, the clinician must elucidate the psychological, physical, and pharmacological factors (Table 61.2) that can contribute to this condition. Unfortunately, a lack of effective therapies is a significant barrier to treatment of DE.

Anejaculation and aspermia
Anejaculation may, for certain patients, be an extreme form of delayed ejaculation, or it may be a different problem entirely. This difference can usually be ascertained from the sexual history, especially if the patient notes orgasm without ejaculation (‘dry orgasm’). The key is to differentiate anejaculation from
Acquired anejaculation may be due to a surgical procedure that also disrupts the normal anatomy of the male reproductive tract. Transurethral resection of the prostate (TURP) and incision of the bladder neck are two surgical procedures that may be implemented in men with LUTS and that can lead to anejaculation. Of course, any surgical injury to the nerve supply involved in ejaculation may also lead to acquired anejaculation. Examples of this would include aortic or para-aortic surgery (abdominal aortic aneurysm, retroperitoneal lymphadenectomy), proctocolectomy, radical prostatectomy, bilateral sympathectomy, or spinal cord injury.\textsuperscript{13} The effect of spinal cord injury on ejaculation has been well established, with an incidence of about 90%. The level and completeness of the injury are factors in the ability of the patient to ejaculate, with lower injuries having a greater chance of preserving function.\textsuperscript{27} Other medical diseases affecting the nervous system may also adversely affect ejaculation, including diabetes mellitus or multiple sclerosis. Hypogonadism and hypothyroidism have been linked to anejaculation as well.\textsuperscript{13}

One final point of the patient interview is to determine if fertility is an issue for the patient. If the patient has solitary anejaculation without other sexual dysfunction, the only indication for intervention is to retrieve sperm for fertility purposes (e.g. by electroejaculation or sperm aspiration).

### Anorgasmia

Orgasm is a centrally mediated, subjective perception of pleasure that normally occurs at the time of ejaculation in men. Anorgasmia, however, may occur with or without ejaculation and should be distinguished from DE, retrograde ejaculation, anejaculation, and aspermia. It is important for the clinician to understand, as well as communicate to the patient, that orgasm and ejaculation are separate processes. It is common for patients and even treating physicians to confuse the two entities.

As described above, several behavioral, religious and cultural, and psychological factors may play a role in inhibiting orgasm (and ejaculation). These may be identified in the patient’s sexual history. Again, assessing whether the symptom is situational or global, acquired or lifelong is helpful, as is determining whether ejaculation is occurring. It is relatively easy to distinguish between primary and secondary anorgasmia through taking a proper sexual and medical history.

Primary anorgasmia or ‘congenital anorgasmia’ occurs when a patient has never experienced an orgasm at any point in his life. It is believed to be an extremely rare condition, occurring in less than 1% of the population.\textsuperscript{28} Although the exact etiology is unknown, it is believed to generally be psychogenic, and nocturnal emissions will still occur. This may be important to verify in the event that sperm retrieval is desired for assisted reproduction.\textsuperscript{29}

Secondary anorgasmia occurs when a patient who at one time did achieve orgasm is currently unable to do so. Unlike primary anorgasmia, which is believed to be usually psychogenic, secondary anorgasmia may have an organic etiology. As with anejaculation, neurologic injury or disease may contribute to anorgasmia, as can drugs such as SSRIs.\textsuperscript{30} Multiple sclerosis and spinal cord injury are common causes of secondary anorgasmia.\textsuperscript{31}

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**Table 61.2 Pharmacologic agents with potential effect on ejaculatory function**

<table>
<thead>
<tr>
<th>Pharmacologic agent</th>
<th>Related disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotonin modifying agents (SSRIs, clomipramine)</td>
<td>Delayed ejaculation, possible retrograde ejaculation</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>Delayed ejaculation, possible retrograde ejaculation</td>
</tr>
<tr>
<td>Methyldopa</td>
<td>Delayed ejaculation, possible retrograde ejaculation</td>
</tr>
<tr>
<td>Monoamine oxidase inhibitors</td>
<td>Delayed ejaculation, possible retrograde ejaculation</td>
</tr>
<tr>
<td>Antipsychotics (e.g. haloperidol)</td>
<td>Delayed ejaculation, possible retrograde ejaculation</td>
</tr>
<tr>
<td>Antiandrogens</td>
<td>Anejaculation, possible low-volume ejaculate</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Delayed ejaculation</td>
</tr>
<tr>
<td>Alpha-receptor antagonists</td>
<td>Retrograde ejaculation</td>
</tr>
</tbody>
</table>

SSRI, selective serotonin reuptake inhibitor

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anorgasmia or retrograde ejaculation. If orgasm is occurring and retrograde ejaculation has been ruled out (see below) then the patient has true anejaculation (aspermia).

Usually the clinician will be able to determine if anejaculation is accompanied by anorgasmia by the patient interview and sexual history. Certainly, the factors mentioned in the section on DE, above, can also impair the patient’s ability to reach ejaculation and orgasm altogether. If the patient is reaching orgasm (a process that occurs centrally) but ejaculation does not occur then organic factors are likely involved. Any medical disease, surgery, or pharmacologic intervention that interferes with central control of ejaculation or the afferent or efferent nerve supply to the vas deferens, bladder neck, pelvic floor, or penis may result in inhibited ejaculation, anejaculation, or anorgasmia.\textsuperscript{11}

The clinician should attempt to determine whether the anejaculation is lifelong or acquired, situational or global. This may provide insight as to whether the patient is experiencing anejaculation due to psychological factors or physiological factors (or possibly both). The patient’s medication list should be reviewed for medications that can inhibit ejaculation or cause retrograde ejaculation. Medications that inhibit contraction of the ejaculatory apparatus, which is mediated by alpha-adrenergic input, can actually cause anejaculation with complete blockade rather than simply retrograde ejaculation.

A complete medical history and directed physical exam is important to determine potential causes of anejaculation. Lifelong anejaculation may be due to a congenital anatomic abnormality. Examples of congenital causes of anejaculation include Mullerian duct cysts, Wolfian duct abnormalities, and prune belly syndrome. Transrectal ultrasound may be necessary to confirm the diagnosis of a Mullerian duct cyst (prostatic urethra).\textsuperscript{30} Congenital absence of the vas deferens may occur in patients with cystic fibrosis or in isolation. However, these patients normally have low-volume ejaculate rather than aspermia, owing to secretions from the prostate.
It is worthwhile to note that some patients do relate a decrease in intensity of orgasm with a decrease in ejaculatory volume. It is known that androgen levels influence seminal fluid formation. Advancing age or any iatrogenic cause of hypogonadism may lead to decreased ejaculatory volume (or even aspermia) and subsequently a reduced perception of sexual pleasure. Thus, some clinicians recommend determining a testosterone level for patients with anorgasmia who may potentially be hypogonadal.

Retrograde ejaculation

Retrograde ejaculation (RE) presents as anejaculation but is diagnosed conclusively by the finding of sperm in the urine on a post-ejaculatory urinalysis (PEU). Unlike delayed or inhibited ejaculation or anorgasmia, retrograde ejaculation occurs from an organic etiology. As with aspermia without anorgasmia, treatment is rarely necessary unless fertility is an issue.

Although a sexual history is still obtained, the patient's medical and surgical history usually provides insight into the diagnosis. As with anejaculation, systemic or neuropathic disease may lead to RE. Autonomic neuropathy from diabetes mellitus or multiple sclerosis has been associated with RE, as has spinal cord injury. The incidence of RE in men with an extensive history of diabetes is high, with one particular study reporting an incidence of 32%.32

Congenital abnormalities such as bladder extrophy may result in incompetence of the bladder neck thus yielding retrograde ejaculation. RE is more commonly iatrogenic from surgical or pharmacologic therapy. The clinician should pay special attention to the patient's list of medications. As with other disorders of ejaculation, RE may be caused by many commonly prescribed drugs such as antidepressants (SSRIs, haloperidol, monoamine oxidase inhibitors, tricyclics) and agents that block alpha-adrenergic function. Urologists and primary care physicians who prescribe alpha-blocker therapy for LUTS commonly see this association. This side-effect of alpha-receptor blocking therapy is seen most commonly with tamsulosin, at a rate of approximately 30%.34 It should be emphasized that ejaculatory disorders are common in men with BPH and LUTS, even those not treated with tamsulosin.23 Although questionnaires are in common use for evaluating LUTS in BPH-prone patients, no questionnaire for the evaluation of ejaculatory disorders has been commonly implemented in these patients despite the prevalence of sexual dysfunction. A 25-item questionnaire has been developed and validated for this purpose and a short form is currently under development.34

Any surgical procedure that compromises closure of the bladder neck may potentially lead to RE. Examples of this would include surgery to the bladder neck itself, such as TURP or bladder neck incision. Rates of RE after these procedures are relatively high but vary; they are estimated to be 25–80%.35,36

As with patients who are apparently anejaculatory from major abdominopelvic or retroperitoneal surgery, RE may be occurring instead.

Since there is extensive overlap in potential causes of anejaculation and RE, the diagnosis of RE may be confirmed or excluded by a PEU. The term 'post-ejaculatory urinalysis' is actually somewhat misleading. Generally it is not known if the patient is truly ejaculating or not (the reason for the test). The majority of patients will experience orgasm so the test is conducted after masturbation or other stimulation to the point of orgasm. The patient then voids and the urine sample is examined for spermatozoa. The presence of sperm confirms the diagnosis of RE, although the minimum number of sperm needed to be seen on PEU has not been defined. In addition, transrectal ultrasound may be performed, which classically would demonstrate an open bladder neck at rest.2

Summary

Ejaculatory disorders are a common disorder, increasing as men age. Despite their prevalence they often go untreated or misdiagnosed by clinicians. Patients may fail to bring up ejaculatory complaints because of embarrassment or a belief that no treatments are available. In turn, clinicians may be reluctant to inquire about these conditions, or be unaware how to diagnose or treat. Once thought to be purely psychological conditions, recent investigation has demonstrated an organic basis for several ejaculatory disorders, with PE receiving extensive attention in recent years. A complete sexual and medical history and a directed physical examination are often essential to diagnose these disorders and categorize them appropriately. Once the treating clinician has determined the diagnosis and possible etiology, the appropriate therapy may be initiated. As awareness and knowledge of the organic basis for these disorders increases, innovative therapies will arise that, when combined with behavioral therapy, can result in effective treatment for these distressing conditions.

REFERENCES

Medical treatment of ejaculatory dysfunction

Chris G McMahon

Introduction

Ejaculatory dysfunction (EjD) is one of the most common male sexual disorders. The spectrum of EjD extends from premature ejaculation (PE), through delayed ejaculation, to a complete inability to ejaculate (anejaculation), and includes retrograde ejaculation and painful ejaculation. The sexual response cycle comprises four interactive, non-linear stages: desire, arousal, orgasm, and resolution. In males, the fourth stage of orgasm is usually coincident with ejaculation, but represents a distinct cognitive and emotional cortical event. EjD is a disruption of the fourth stage of orgasm.

Physiology of ejaculation

Ejaculation is a reflex comprising sensory receptors and areas,afferent pathways, cerebral sensory areas, cerebral motor centers, spinal motor centers, and efferent pathways. There are three basic mechanisms involved in normal antegrade ejaculation – emission, ejection and orgasm.1 Emission is the result of a sympathetic spinal cord reflex initiated by genital or cerebral erotic stimuli (or both) and involves the sequential contraction of accessory sexual organs. Considerable initial voluntary control of emission progressively decreases until the point of ejaculatory inevitability.2 Ejection also involves a sympathetic spinal cord reflex over which there is little or no voluntary control. Ejection involves bladder neck closure; rhythmic contractions of bulbocavernous, bulbospongiosus and other pelvic floor muscles; and relaxation of the external urinary sphincter.3 Orgasm is the result of cerebral processing of pudendal nerve sensory stimuli resulting from increased pressure in the posterior urethra, sensory stimuli arising from the veramontanum, and contraction of the urethral bulb and accessory sexual organs.

The ejaculatory reflex is predominantly controlled by a complex interplay between central serotonergic and dopaminergic neurons with secondary involvement of oxytocinergic, cholinergic, adrenergic, nitrergic, galanergic, and GABAergic neurons. The cerebral events that occur during ejaculation and the abnormalities present in men with PE have not been clearly defined with positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) brain imaging techniques. Seminal emission and ejection are integrated into the complex pattern of copulatory behavior by several forebrain structures, including the medial preoptic area (MPOA) and the nucleus paragigantocellularis (nPGi) (Figure 62.1).4,5 Descending serotonergic pathways from the nPGi to the lumbosacral motor nuclei tonically inhibit ejaculation.6 Disinhibition of the nPGi by the MPOA facilitates ejaculation. A population of lumbar spinothalamic (LSt) neurons has been identified in male rats, which constitute an integral part of the generation of ejaculation. LSt cells send projections to the autonomic nuclei and motor neurons involved in the emission and expulsion phase, and they receive sensory projections from the pelvis.7 Several brain areas are activated after ejaculation by ascending fibers from the spinal cord and may have a possible role in satiety and the post-ejaculatory refractory time.

Animal and human sexual psychopharmacological studies have attributed a serotonergic basis and possible genetic etiology to PE.6-9 Male rat studies demonstrate that serotonin (5-hydroxytryptamine, 5-HT) and 5-HT receptors are involved in the ejaculatory process. The speed of ejaculation appears to be determined by 5-HT-2C and 5-HT-1A receptors. Stimulation of 5-HT-2C receptors with non-selective 5-HT-2C agonists delays ejaculation in male rats whereas stimulation of postsynaptic 5-HT-1A receptors results in shorter ejaculation latency.10 Administration of selective serotonin reuptake inhibitors (SSRIs) results in active blockade of presynaptic membrane 5-HT transporters, and the resultant higher synaptic cleft levels of 5-HT activate postsynaptic 5-HT-2C and 5-HT-1A receptors and delay ejaculation.7,11

Premature ejaculation

The American Psychiatric Association’s Diagnostic and Statistical Manual, 4th edition, text revision (DSM-IV-TR) defines PE as ‘… persistent or recurrent ejaculation with minimal stimulation before, on, or shortly after penetration, and before the person wishes it’. DSM-IV-TR goes on: ‘The clinician must take into account factors that affect duration of the excitement phase (such as age, novelty of the sexual partner or situation, and recent frequency of sexual activity); whether the disturbance causes marked distress or interpersonal difficulty; and whether the PE is not due exclusively to the direct effects of a substance (e.g., withdrawal from opioids).’12 This multivariate definition is manifestly inadequate, with a low predictive value for PE,13 but it does encompass the
main dimensions of PE – ejaculatory latency, control, sexual satisfaction, and distress.

**Epidemiology of premature ejaculation**

PE is often reported, perhaps erroneously, as one of the most common male sexual disorders, and has been estimated to occur in 4–39% of men in the general community. However, it remains poorly defined and inadequately characterized. As a result, there is a substantial disparity between the reported incidence of PE in many epidemiological studies (which rely heavily on self-reported PE) and the incidence suggested by community-based normative stopwatch intravaginal ejaculatory latency time (IELT) studies.

Most community-based epidemiological studies are limited by their reliance on either patient self-report of PE or inconsistent and poorly validated definitions of PE. A recent multinational, community-based, age-ranging study of an unselected ‘normal’ population of 500 heterosexual couples, which involved stopwatch timing of the IELT during sexual intercourse, has provided previously lacking normative data. This study demonstrated that the distribution of the IELT was positively skewed, with a median IELT of 5.4 minutes (range, 0.55–44.1 minutes) (Figure 62.2). The median IELT decreased with age and varied between countries. The authors regarded the 0.5 and 2.5 percentiles as acceptable standards of disease definition in this type of skewed distribution, and proposed that men with an IELT of less than 1 minute (belonging to the 0.5 percentile) have ‘definite’ PE, while men with IELTs between 1 and 1.5 minutes (between 0.5 and 2.5 percentile) have ‘probable’ PE.

In a study of 1326 consecutive men with PE, lifelong PE was present in 736 men (74.4%), and acquired PE was present in 253 men (25.6%). Men with PE appear younger than those without, and after adjusting for concomitant erectile dysfunction (ED) the risk of PE significantly decreased with aging. Higher levels of education, divorce, and the presence of social phobia appear to increase the risk of PE. A decreased risk of PE has been reported in men with treated diabetes, and no association was found with hypertension, cardiac disease, hypercholessterolemia, and peripheral or central neuropathy. Men with self-reported PE have a lower frequency of sexual intercourse and higher levels of intercourse-related anxiety, and they note greater impairment in intercourse satisfaction and sexual relationship satisfaction compared with men without PE. However, they do not report a reduced quality of life, reduced sexual desire, or a reduced ability to become sexually aroused.

There are few published data on impact of birth country, religion, or culture on the prevalence of PE. An increased susceptibility to PE in men from the Indian subcontinent has been reported. Kinsey’s observation that Asian men have shorter times to ejaculation than Caucasian men, who in turn have shorter times to ejaculation than Afro-Caribbean men, has been interpreted to suggest that some races are more ‘sexually restrained’ than others. A recent study reported a preponderance of men from Middle Eastern and Asian backgrounds presenting for treatment of PE which exceeded the representation of these ethnic groups in the local population.

**Classification of premature ejaculation**

The premise that PE is a psychosomatic disturbance and due to a psychologically overanxious personality was first suggested...
by Schapiro in 1943. He classified PE as either primary (lifelong) or secondary (acquired). The behavioristic view that chronic PE was the result of performance anxiety related to a disturbing initial episode of PE was first proposed by Masters and Johnson. Most of the behavioral treatments currently used are based on this premise. Waldinger has extended Schapiro’s classification to include lifelong PE, acquired PE, natural variable PE, and premature-like ejaculatory dysfunction (EjD) (Table 62.1).

Lifelong PE is a syndrome characterized by a cluster of core symptoms including early ejaculation at nearly every intercourse, within 30–60 seconds in the majority of cases (80%) or between 1–2 minutes (in 20%), with every or nearly every sexual partner and from the first sexual encounters onwards.

Acquired PE differs in that sufferers develop early ejaculation at some point in their life having previously had normal ejaculation experiences; it may be due to psychological or relationship problems, ED, prostatitis or thyroid dysfunction.

In natural variable PE, the ejaculation time is never consistently rapid but merely coincidentally and situationally rapid. This type of PE should not be regarded as a normal variation in sexual performance and is characterized by inconsistent and irregular early ejaculation, often with reduced ejaculatory control.

Men with premature-like ejaculatory dysfunction complain of PE but have a normal ejaculatory latency of 3–6 minutes. It is characterized by a preoccupation with a subjective perception of rapid ejaculation, with an IELT within the normal range, but often with reduced ejaculatory control.

### Table 62.1 The four premature ejaculation (PE) syndromes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lifelong premature ejaculation</th>
<th>Acquired premature ejaculation</th>
<th>Natural variable premature ejaculation</th>
<th>Premature-like ejaculatory dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>IELT</td>
<td>Very short IELT (&lt;1–1.5 minutes)</td>
<td>(Very) short IELT (&lt;1.5–2 minutes)</td>
<td>Normal IELT (3–8 minutes)</td>
<td>Normal or long IELT (3–30 minutes)</td>
</tr>
<tr>
<td>Frequency</td>
<td>Consistent</td>
<td>(In)consistent</td>
<td>Inconsistent</td>
<td>(In)consistent</td>
</tr>
<tr>
<td>Etiology</td>
<td>Neurobiological and genetic</td>
<td>Medical and/or psychological</td>
<td>Normal variation of ejaculatory performance</td>
<td>Psychological</td>
</tr>
<tr>
<td>Treatment</td>
<td>Medication with or without counseling</td>
<td>Medication and/or psychotherapy</td>
<td>Psychoeducation, reassurance</td>
<td>Psychotherapy</td>
</tr>
<tr>
<td>Prevalence</td>
<td>Low (?)</td>
<td>Low (?)</td>
<td>High (?)</td>
<td>High (?)</td>
</tr>
</tbody>
</table>

IELT, intravaginal ejaculation latency time. From Drugs 2007; 67: 547–63.

### Defining premature ejaculation

Medical literature contains several univariate and multivariate operational definitions of PE. The definitions of PE in DSM-IV-TR and the International Classification of Diseases (ICD)-10 of the World Health Organization differ substantially and are authority-based and not evidence-based, having no support from controlled clinical trials or epidemiological studies. This lack of agreement as to what constitutes PE has hampered basic and clinical research into the etiology and management of this condition. Quantitative measures of
intercourse, such as the IELT, and subjective measures such as voluntary control over ejaculation or self-efficacy, the extent of patient sexual satisfaction and the level of bother or distress, have been employed as patient reported outcomes (PROs) in PE clinical trials. Each of the three criteria above has been operationalized, although not always with consistency.44

**Intravaginal ejaculatory latency time**

Operation alization of PE using the length of time between penetration and ejaculation, the IELT, forms the basis of most current clinical studies on PE. There is considerable variance of the latencies used to identify men with PE, with IELTs ranging from 1 to 7 minutes, and none of the definitions is based on normative data or offers any supportive rationale for their proposed cut-off time.45-48 An average duration of intercourse of 4–7 minutes was reported by Gebhard, suggesting that ejaculation before 4 minutes after intromission should be considered premature.49

IELT is measured by a stopwatch operated by the partner. Treating physicians must interpret patient self-report of PE and self-estimation of IELT with some caution, since the estimation of ejaculatory latency by men and women may correlate poorly with stopwatch-recorded IELT. However, several authors have reported that patient self-estimation of IELT correlates reasonably well with subsequent stopwatch IELT.50-52

Waldinger et al. reported IELTs of less than 30 seconds and less than 60 seconds in 77% and 90% of 110 men with PE, respectively.53 McMahon et al. reported similar results in 1346 consecutive men with PE and a mean IELT of 43.4 seconds.23 Predominant anteportal ejaculation (during foreplay) occurred in 5.6% of men. Recent normative data parallel these findings in demonstrating a median IELT of 5.4 minutes and suggests that men with an IELT of less than 1 minute have ‘definite’ PE, while men with IELTs between 1 and 1.5 minutes have ‘probable’ PE.22

**Voluntary control**

Kaplan and other authors have suggested that an inability to defer ejaculation voluntarily defines PE.54-57 Patrick et al. reported ratings of ‘very poor’ or ‘poor’ for control over ejaculation in 72% of men with PE compared with 5% in a group of normal controls.58 However, control is a subjective measure that is difficult to translate into quantifiable terms, and it is the most inconsistent dimension of PE. Control has yet to be adequately operationalized to allow comparison across subjects or across studies. Grenier and Byers failed to demonstrate a strong correlation between ejaculatory latency and subjective ejaculatory control.14 Several authors report that diminished control is not exclusive to men with PE and that some men with a brief IELT report adequate ejaculatory control and vice versa, suggesting that the dimensions of ejaculatory control and latency are distinct concepts.18,59 Furthermore, there is a higher variability in changes in control compared with IELT in men treated with SSRIs.59

However, Rosen et al. report that control over ejaculation, personal distress, and partner distress was more influential in determining PE status than IELT.5 In addition, the effect of IELT upon satisfaction and distress appears to be mediated via its direct effect upon control.60 Clearly, the patient’s perception of control over ejaculation is central to understanding how PE is associated with satisfaction with sexual intercourse and ejaculation-related distress.

**Sexual satisfaction**

Men with PE report lower levels of sexual satisfaction than men with normal ejaculatory latency. Patrick et al. reported ratings of ‘very poor’ or ‘poor’ for sexual satisfaction in 31% of men with PE compared to 1% in a group of normal controls.29 The inability to control and defer ejaculation until the female partner was sexually satisfied on at least 50% of intercourse attempts was proposed as a definition of PE by Masters and Johnson.61 An inherent problem exists here in defining a man as dysfunctional based on the sexual responsiveness of his partner. This definition implies that any male whose female partner has difficulty in reaching orgasm should be labeled as a premature ejaculator. This definition is at odds with the report that only 30% of women achieve orgasm during sexual intercourse regardless of the extent of their partner’s ejaculatory control and latency. Rowland reported that over 89.4% of men with self-reported PE regarded fulfilling their partner’s sexual needs as very or extremely important.62

However, caution should be exercised in attributing improved satisfaction solely to the effect of drug treatment, and contributions from other difficult-to-quantify issues such as intimacy, friendship, sexual attraction, and communication should not be ignored. Furthermore, men with PE are easily pleased and report improved satisfaction with minimal improvements in IELT. There is an inherent problem in using sexual satisfaction as a measure of treatment efficacy. It is at best a surrogate for treatment efficacy and must be regarded as a ‘soft’ study end-point compared to objective end-points.

**Distress**

Existing definitions of PE include distress as an important dimension of PE.12,43,63 However, the word ‘distress’ has negative social implications and its existence is denied by most men with PE. This dimension of PE is better captured by the word ‘bother’. One study reported that 64% of men with PE rated their extent of personal distress as ‘quite a bit’ or ‘extreme’ compared to 4% in a group of normal controls.58 The extent of psychological impact on patients, partners, and the overall relationship are perhaps the most important aspects of treatment-seeking behavior and best define the severity of PE.

Although partner distress is a significant contributor to treatment-seeking behavior, there is limited information regarding the effect of PE on the partner. Several studies have reported that the effects of PE on the female partner are integral to understanding the impact of PE on the male and on the sexual relationship as a whole.64-66 Patrick et al. reported that 44% of partners of men with PE rated their extent of personal distress as ‘quite a bit’ or ‘extreme’ compared to 3% in a group of partners of normal controls.66 Patrick et al. also reported
that partner PRO measures differentiated men with PE from men without PE and correlated moderately with measures of IELT and subject PRO measures. However, partner perceptions of PE generally indicated less dysfunction than those of subjects.39 Although PE adversely affects partner satisfaction, it appears to have minimal impact upon relationship satisfaction.50 Furthermore, partners of men with PE report relatively high levels of female sexual dysfunction.67,68 The observation that PE often pre-dates the time of onset of the women’s sexual symptoms suggests that PE may be a risk factor for female sexual dysfunction.67

The design of all future studies on any aspect of PE should include a uniform operationalized multivariate definition of PE in which the dimensions of latency, control, satisfaction, and distress or bother are defined, measured, and analyzed as continuous variables without arbitrary cut-off values.

The etiology of premature ejaculation

Historically, attempts to explain the etiology of PE have included a diverse range of biological and psychological theories. Most of these proposed etiologies are not evidence-based and are speculative at best. Psychological theories include the effect of early experience and sexual conditioning, anxiety, sexual technique, the frequency of sexual activity, and psychodynamic explanations. Biological explanations include evolutionary theories, penile hypersensitivity, central neurotransmitter levels and receptor sensitivity, degree of arousability, the speed of the ejaculatory reflex, and the level of sex hormones.

There is little empirical evidence to suggest a causal link between PE and any of the factors thought to cause PE. There is, however, limited correlational evidence to suggest that lifelong PE is a genetically determined biological variable related to the inherited sensitivity of central 5-HT receptors and that acquired PE is due to high levels of sexual anxiety, ED, or lower urinary tract infection.

Ejaculatory latency time is probably a biological variable, which is genetically determined and may differ between populations and cultures, ranging from extremely rapid through average to slow ejaculation. Hyposensitivity of the 5-HT-2C or hypersensitivity of the 5-HT-1A receptors (or both) have been suggested as possible explanations of lifelong PE.11,69 Men with low 5-HT neurotransmission and probable 5-HT-2C receptor hyposensitivity may have their ejaculatory threshold genetically ‘set’ at a lower point and ejaculate quickly with minimal stimulation, whereas men with a higher set-point can sustain more prolonged and higher levels of sexual stimulation and can exert more control over ejaculation. Men with a very high set-point may experience delayed or absent ejaculation despite achieving a full erection and prolonged sexual stimulation. Treatment with an SSRI activates the 5-HT-2C receptor, elevates the ejaculatory threshold set-point, and delays ejaculation. The extent of ejaculatory delay may vary widely in different men according to the dosage and frequency of administration of the SSRI and the genetically determined ejaculatory threshold set-point. Cessation of treatment results in re-establishment of the previous set-point within 5–7 days in men with lifelong PE.

Anxiety has been reported as a cause of PE by multiple authors and is entrenched in the folklore of sexual medicine as the most likely cause of PE despite scant empirical research evidence to support any causal role.34,42,70 Several authors have suggested that anxiety activates the sympathetic nervous system and reduces the ejaculatory threshold as a result of an earlier emission phase of ejaculation.34,70 The possibility that high levels of anxiety and excessive and controlling concerns about sexual performance and potential sexual failure might distract a man from monitoring his level of arousal and recognizing the prodromal sensations that precede ejaculatory inevitability has been suggested as a possible cause of PE by several authors.54,69,71–74 The causal link between anxiety and PE is speculative, is not supported by any empirical evidence, and is in fact contrary to empirical evidence, from some researchers.75

Recent data demonstrate that almost half of men with ED also experience PE.38 Men with early ED may intentionally ‘rush’ sexual intercourse to prevent premature loss of their erection and ejaculate with a brief latency. This may be compounded by the presence of high levels of performance anxiety related to their ED, which serves only to worsen the prematurity. In the absence of a thorough sexual history, these men may be incorrectly diagnosed as suffering from PE and not the underlying ED.

Premature ejaculation drug trial design

The results of PE clinical drug trials are only reliable, interpretable, and capable of being generalized to patients with the disorder studied when conducted in well-defined and consistent populations, using a double-blind placebo-controlled study design, and consistent objective physiological measures or sensitive, validated outcome assessment instruments as study end-points.27 Subjects with lifelong and acquired PE should be treated as separate PE subgroups, and subjects with ED or other co-morbid sexual disorders should be either excluded or treated as a separate subgroup.

In PE studies, the study population should be well characterized, representative of the overall patient population, and defined using a multivariate definition of PE. As the population of men with PE is not homogeneous, lifelong and acquired PE should be treated as demographically and etiologically distinct disorders and analyzed as separate PE subgroups.23 Subjects should be involved in a stable, monogamous, heterosexual relationship, prepared to attempt intercourse on a regular basis and to provide written informed consent. The presence of comorbid ED should be evaluated using a validated instrument such as the International Index of Erectile Function (IIEF) and patients with any degree of ED should be either excluded from the study or treated as a separate subgroup. Patients with hypoactive sexual desire or other sexual disorders, urogenital infection, major psychiatric disorders, a history of drug and alcohol abuse, or contraindications to the study drug should be excluded from the study.

Measurement of the IELT by stopwatch is the best method to diagnose PE and the response to treatment, and should be used as a primary efficacy end-point and reported as the fold increase of median IELT over pre-treatment IELT. It is well recognized that IELT in both the general population and in
men with PE is distributed in a positively skewed pattern.\textsuperscript{21,23} Waldinger’s assertion that reporting arithmetic means overestimates both baseline and end-point IELTs and his suggestion that either the median or geometric mean IELT values are more representative of treatment response are well-founded.\textsuperscript{26,27} The arithmetic mean IELT may exceed median values by as much as 45%.\textsuperscript{23} Furthermore, because a typical study population has a broad range of baseline IELT values (0–90 seconds), reporting mean raw study-end IELT is confusing since it incorrectly suggests that all men respond to that extent. The study-end fold increase in median or geometric mean IELT is more representative of true treatment outcome and must be regarded as the contemporary universal standard.

Laboratory studies of EjD may be simplified by the use of the Sexual Assessment Monitor (SAM), an electronic data collector that comprises a vibrator to induce ejaculation and a sensor to measure time to erection and IELT by the detection of ejaculatory pulses, but the role of such devices in large at-home phase 3 clinical trials is limited.\textsuperscript{26} Recent normative IELT data support earlier suggestions by several authors that IELTs of less than 1 minute or less than 2 minutes be regarded as cut-off points for inclusion in a clinical trial.\textsuperscript{21,14,76}

Subjective PROs of ejaculatory control, sexual satisfaction, and bother or distress are important additional efficacy endpoints and can be evaluated using validated PRO instruments.\textsuperscript{58,79–80} Symonds et al. report the development and validation of a brief self-administered five-item questionnaire, the Premature Ejaculation Diagnostic Tool (PEDT), to diagnose PE in clinical trials.\textsuperscript{82} A pilot development tool of nine questions was derived from qualitative research involving focus-group and individual interviews of men with either physician-diagnosed or self-reported PE; this research was psychometrically analyzed and distilled into a five-item, 0–25 score, unidimensional measure that captures the essence of DSM-IV-TR and the dimensions of control, satisfaction, personal distress, and interpersonal distress. The PEDT has good convergent validity and re-test reliability, and sensitivity–specificity analysis suggests that a score ≥11 indicates PE.\textsuperscript{83} The PEDT is limited in several respects, but represents a significant development towards simplifying the methodology of PE drug studies. Future development of this diagnostic tool would be incomplete without further validation of this tool to determine the potential relationship between score, severity of PE, and response to treatment.

The reliability of stopwatch IELT alone in assigning PE status, the use of PROs to replace stopwatch IELT, or the predictive value of single-item PRO measures compared with multiple-item measures are incompletely understood issues. PRO measures, while providing important information, are at best subjective and relate to highly interpretable and imprecise dimensions of ejaculation, and their significance is weighted differently for different patients. On the other hand, IELT may not adequately categorize patients since some patients with a brief IELT report little or no bother and are therefore asymptomatic and so not ‘suffering’ from PE. Clearly, none of the dimensions of PE can universally distinguish men with PE from non-PE men. The current consensus is that a combination of stopwatch IELT and a validated PRO of control, satisfaction, personal distress, and interpersonal distress can adequately identify PE status in prevalence studies and in the screening phase of drug trials, and can measure response to treatment.

Clinical drug trial design in sexual medicine has largely relied on retrospective reporting of adverse effects after an interval of up to 4 weeks, with the consequence that patient recall of the details, frequency, severity, duration, and temporal relationship of adverse events to dosing may be unreliable. It has been suggested that adverse events be reported prospectively in a patient diary within 24 hours using a validated questionnaire, such as the UKU side-effect rating scale, and this would represent a significant advance in basic clinical trial design.\textsuperscript{77,90}

**Treatment of premature ejaculation**

Over the past 15 years, an increasing number of publications have reported the pharmacological treatment of PE with a variety of different medications, which act centrally or locally to retard the psychoneurological control of ejaculation and subsequent orgasm.\textsuperscript{65} It is well established that major tranquillizers and SSRIs retard ejaculation significantly and will, in a small percentage of men, result in anejaculation.\textsuperscript{54,91} The efficacy of SSRIs in delaying ejaculation combined with the low side-effect profile make them first-line agents for PE, administered either on a daily or an on-demand basis.\textsuperscript{76,94}

**Psychosexual counseling**

In many relationships, PE causes few if any problems. In others, the couple may reach an accommodation of the problem through various strategies – young men with a short refractory period may often experience a second and more controlled ejaculation during a subsequent episode of lovemaking. Frequently however, PE eventually leads to significant relationship problems, with the partner regarding the man as selfish and developing a pattern of sexual avoidance. This only worsens the severity of the prematurity on the occasions when intercourse does occur.

The cornerstones of behavioral treatment are the Seman’s ‘stop–start’ maneuver and its modification proposed by Masters and Johnson, the squeeze technique. Both are based on the theory that PE occurs because the man fails to pay sufficient attention to pre-orgasmic levels of sexual tension.\textsuperscript{63,95} As most men with PE are aware of their anxiety and the sources of that anxiety tend to be relatively superficial, treatment success with these behavioral approaches is relatively good in the short term but convincing long-term treatment outcome data are lacking.\textsuperscript{45,96–98}

**Pharmacological treatment**

Pharmacological modulation of ejaculatory threshold represents a novel and refreshing approach to the treatment of PE and a radical departure from the psychosexual model of treatment, previously regarded as the cornerstone of treatment. The introduction of the SSRIs has revolutionized the approach to and treatment of PE. SSRIs encompass five compounds: citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline, all with a similar pharmacological mechanism of action.
Although the methodology of the initial drug treatment studies was rather poor, later double-blind and placebo-controlled studies replicated the genuine effect of clomipramine and SSRIs to delay ejaculation. In spite of a development towards more evidence-based drug treatment research, the majority of studies still lack adequate design and methodology. A recent meta-analysis of all drug treatment studies demonstrated that only 14.4% had been performed according to the established criteria of evidence-based medicine, and that open-design studies and studies using subjective reporting or questionnaires showed a higher variability in ejaculation delay than double-blind studies in which the ejaculation delay was prospectively assessed with a stopwatch.

Daily treatment with selective serotonin reuptake inhibitors

Daily treatment can be performed with paroxetine 20–40mg, clomipramine 10–50mg, sertraline 50–100mg, or fluoxetine 20–40mg (Figure 62.3). Paroxetine appears to exert the strongest ejaculation delay, increasing IELT approximately 8.8-fold over baseline. Ejaculation delay usually occurs within 5–10 days but may occur earlier. Adverse effects are usually minor, start in the first week of treatment, and gradually disappear within 2–3 weeks; they include fatigue, yawning, mild nausea, loose stools, and perspiration. Diminished libido or mild ED is infrequently reported. Significant agitation is reported by a small number of patients and treatment with SSRIs should be avoided in men with a history of bipolar depression.

Daily treatment with alpha-1-adrenoceptor antagonists

Ejaculation is a sympathetic spinal cord reflex that could theoretically be delayed by alpha-1-adrenoceptor blockers. Several authors have reported their experience with the selective alpha-1-blockers alfuzosin and terazosin in the treatment of PE. In a double-blind, placebo-controlled study, Cavallini reported that alfuzosin (6 mg/day) and terazosin (5 mg/day) were effective in delaying ejaculation in approximately 50% of the cases. Similarly, Basar reported that terazosin was effective in 67% of men. However, both studies were limited by the use of subjective study end-points of patient impression of change and sexual satisfaction, and neither evaluated objective end-points such as IELT.

However, in the rat model, systemic injection of tamsulosin impaired bulbospongious muscle contractile capacity and bladder neck and seminal vesicle pressures, whereas alfuzosin did not. Consistent with this, Hellstrom et al. reported decreased ejaculate volume in almost 90% of subjects and anejaculation in approximately 35% of participants with tamsulosin, but he failed to observe anejaculation with alfuzosin. Contrary to these results, a comparison of tamsulosin with alfuzosin in men symptomatic BPH and normal ejaculatory latency demonstrated minimal ejaculatory dysfunction. Additional controlled studies are required to determine the role of alpha-1-blockers in the treatment of PE.

On-demand treatment with selective serotonin reuptake inhibitors

Administration of clomipramine, paroxetine, sertraline, or fluoxetine 4–6 hours before intercourse is efficacious and well tolerated but is associated with less ejaculatory delay than daily treatment. Daily administration of an SSRI is associated with superior increases in IELT compared with on-demand administration, owing to the greatly enhanced 5-HT neurotransmission resulting from several adaptive processes, which may include presynaptic 5-HT-1A and 5-HT-1B or 5-HT-1D receptor desensitization (Figure 62.4). On-demand treatment may be combined with either an initial trial of daily treatment or concomitant low-dose daily treatment.

The assertion that on-demand drug treatment of PE is preferable to daily dosing parallels the rationale for the treatment of ED but is contrary to personal experience and the

Figure 62.3 Selective serotonin reuptake inhibitors produce ejaculatory delay within 5–10 days. IELT, intravaginal ejaculatory latency time. From J Clin Psychopharmacol 1998; 18: 274–81.
results of the only PE drug preference study. Whilst many men suffering from PE who infrequently engage in sexual intercourse may prefer on-demand treatment, the majority of men in established relationships prefer the convenience of daily medication.

On-demand treatment with dapoxetine
A number of rapid-acting, short half-life SSRIs are under investigation as on-demand treatments for PE. Dapoxetine is an SSRI and was originally developed as a short half-life drug for the treatment of depression. In December 2004, a new drug application was submitted to the Food and Drug Administration in the USA for dapoxetine hydrochloride as a drug to treat PE. Dapoxetine is a potent SSRI (binding affinity, pKi=8 nM), structurally similar to fluoxetine. Equilibrium radioligand binding studies using human cells demonstrate that dapoxetine binds to 5-HT, norepinephrine and dopamine reuptake transporters and inhibits uptake in the following rank order of potency: 5-HT> norepinephrine >> dopamine. Brain PET studies have demonstrated significant displaceable binding of radiolabeled dapoxetine in the cerebral cortex and subcortical gray matter.

Dapoxetine undergoes rapid absorption and elimination, resulting in minimal accumulation, and it has dose-proportional pharmacokinetics, which are unaffected by multiple dosing. The pharmacokinetic profile of dapoxetine suggests that it is a candidate for on-demand treatment of PE. The pharmacokinetics of both single doses and multiple doses over 6–9 days (30mg, 60mg, 100mg, 140mg, or 160mg) have been evaluated. Dapoxetine has a time to maximum concentration of 1.4–2.0 hours, and it rapidly achieves peak plasma concentration following oral administration. Both plasma concentration and area under the curve (AUC) are dose-dependent up to 100mg. The mean half-life of dapoxetine after a single dose is 0.5–0.8 hours and plasma concentrations rapidly decline to about 5% of peak plasma concentration at 24 hours. The pharmacokinetics of dapoxetine and its metabolites were not affected by repeated daily dosing, and stable plasma concentrations were reached within 4 days, with only modest accumulation of dapoxetine (approximately 1.5-fold).

Food does not have a clinically significant effect on dapoxetine pharmacokinetics.

No drug–drug interactions associated with dapoxetine have been reported. Co-administration of dapoxetine with ethanol did not produce significant changes in the pharmacokinetics of dapoxetine and its metabolites. Drug interaction studies demonstrate that tadalafil, a phosphodiesterase (PDE) type 5 inhibitor used in the treatment of ED, did not affect the pharmacokinetics of dapoxetine, whereas sildenafil increased the dapoxetine AUC by 22%. However, this was not regarded as clinically important. Dapoxetine did not appear to affect the pharmacokinetics of tadalafil or sildenafil.

Preliminary data suggest that dapoxetine administered 1–2 hours prior to planned intercourse is modestly effective and well tolerated, superior to placebo, and increases IELT.
two- to three-fold over baseline in a dose-dependent fashion (Figure 62.5). In randomized, double-blind, placebo-controlled, multicenter, phase 3 12-week clinical trials involving 2614 men with a mean baseline IELT ≤2 minutes, dapoxetine 30mg or 60mg was more effective than placebo for all study end-points. Mean IELT increased from 0.91 minutes at baseline to 2.78 minutes (3.0-fold) and 3.32 minutes (3.6-fold) at study end with dapoxetine 30mg and 60mg, respectively, compared with a 1.9-fold increase with placebo. Mean patient rating of control over ejaculation as fair, good, or very good increased from 2.8% at baseline to 51.8% and 58.4% at study end with dapoxetine 30mg and 60mg, respectively. Treatment-related side effects were uncommon and dose-dependent; they included nausea, diarrhea, headache, and dizziness, and they were responsible for study discontinuation in 4% (30mg) and 10% (60mg) of subjects.

However, Waldinger et al. have suggested that dapoxetine-induced ejaculation delay is marginal and has been systematically overestimated by the misleading use of arithmetic mean IELTs as opposed to geometric mean IELTs or median IELTs.

Figure 62.5 (a) Dapoxetine increased intravaginal ejaculatory latency time (IELT) from 0.91 minutes at baseline to 2.78 and 3.32 minutes at study end with dapoxetine 30mg and 60mg, respectively. (b) Percentage of subjects rating control over ejaculation as fair, good, or very good increased from 3.1% at baseline to 51.8% and 58.4% at study end with dapoxetine 30mg and 60mg, respectively. (c) Percentage of subjects rating sexual satisfaction as fair, good, or very good increased from 53.6% at baseline to 70.9% and 79.2% with dapoxetine 30mg and 60mg, respectively. (Rating scale 0–5 scale, where 0 is very poor and 5 is very good.) From Lancet 2006; 368: 929–37.
at study end. They assert that the use of median IELTs at study end would result in a substantially lower study end IELT fold increase of 1.2, 1.9 and 2.3 for placebo, dapoxetine 30mg, and dapoxetine 60mg, respectively. This is of marginal clinical significance, is only slightly higher than the 1.4-fold increase of placebo and is substantially less than the 8.8-fold increase seen with daily dosing of paroxetine. Walderinger et al. also assert that the dapoxetine phase 3 study lacks an adequate methodology of assessment of dapoxetine-related adverse effects, since adverse effects were retrospectively assessed with a non-validated questionnaire at each monthly visit to the clinic. They cite the disparity between the incidence of dapoxetine adverse effects in volunteer control pharmacokinetic studies and the dapoxetine phase 3 study as consistent with this aspect of inadequate study design and the risk of underestimating the incidence of adverse effects like dizziness, headache, and diarrhea.

It is likely that dapoxetine, despite its modest effect upon ejaculatory latency, has a place in the management of PE, which will eventually be determined by market forces once the challenge of regulatory approval has been met.

On-demand treatment with tramadol
The efficacy of on-demand tramadol in the treatment of PE was recently reported. Tramadol is a centrally acting synthetic opioid analgesic with an unclear mode of action that is thought to include binding of parent and M1 metabolite to micro-opioid receptors and weak inhibition of reuptake of norepinephrine and 5-HT. Serotonin syndrome has been reported as an adverse effect of tramadol alone or in combination with SSRIs. In a double-blind, placebo-controlled study, the on-demand use of tramadol 50mg, taken 2 hours prior to intercourse, exerted a clinically relevant ejaculation delay in men with PE with a 12.7-fold increase in IELT. In a single-blind, placebo-controlled study, the on-demand use of tramadol 25mg, taken 1–2 hours prior to intercourse, was associated with a 6.3-fold increase in IELT. Additional flexible dose studies and long-term follow-up studies to evaluate the risk of opioid addiction are required.

Anesthetic topical ointments
The use of topical local anesthetics such as lidocaine and prilocaine as a cream, gel, or spray is well established and is moderately effective in retarding ejaculation. A recent study reported that a metered-dose aerosol spray containing a eutectic mixture of lidocaine and prilocaine produced a 2.4-fold increase in baseline IELT and significant improvements in ejaculatory control and in both patient and partner sexual quality of life. They may be associated with significant penile hypoesthesia and possible transvaginal absorption, resulting in vaginal numbness and resultant female anorgasmia unless a condom is used.

Intracavernous injection of vasoactive drugs
Intracavernous self-injection treatment of PE has been reported but is without any evidence-based support for the efficacy of this strategy. Fein reported an open study of eight men treated with a combination of papaverine and phen tolamine administered by intracavernous auto-injection in which the treatment success was defined as prolongation of erection after ejaculation and not by any measure of ejaculatory latency. Three of eight men stated that they were cured and suspended treatment while the other five men continued using the medication. In the absence of well-controlled studies, treatment of PE by intracavernous auto-injection cannot be recommended.

Phosphodiesterase type 5 inhibitors
Medications that inhibit PDE-5 isoenzyme — sildenafil, tadalafil, and vardenafil — are effective treatments for ED. Several authors have reported their experience with PDE-5 inhibitors alone or in combination with SSRIs as a treatment for PE. The putative role of PDE-5 inhibitors as a treatment for PE is based upon the role of the nitric oxide (NO)–cGMP transduction system as a central and peripheral mediator of inhibitory non-adrenergic, non-cholinergic nitricergic neurotransmission in the urogenital system. Several studies suggest that elevation of extracellular NO in the MPOA accelerates dopamine release and facilitates male copulatory behavior of rats, whereas a decrease of NO reduces their copulatory behavior. Hull et al. demonstrated that microinjection of the NO synthase (NOS) inhibitor, N-nitro-L-arginine methyl ester (NAME) decreased the number of erections, but also increased the number of seminal emissions and decreased the latency to the first seminal emission. The results indicate that not only does NO promote erection in intact male rats, but it may also inhibit seminal emission.

NOS isoenzymes are present in human seminal vesicle smooth muscle. Several authors have reported the effects of NO donor drugs on electrically induced contractions and on tissue levels of cGMP and cAMP in isolated human seminal vesicle smooth muscle preparations and have concluded that NO might be involved in the control of secretory activity and smooth muscle function of human seminal vesicles. Consistent with this, Kriegsfeld reported that mice homozygous for endothelial NOS (eNOS) gene deletion have striking ejaculatory anomalies. A significantly higher percentage of eNOS gene deletion mice than normal controls ejaculated during the testing period, requiring less stimulation and fewer mounts and intromissions.

A recent systematic review of 14 studies published in peer-reviewed journals or the proceedings of major international and regional scientific meetings on the PDE-5 inhibitor treatment for PE examined the role of NO as a neurotransmitter involved in the central and peripheral control of ejaculation, the methodology of PDE-5 inhibitor treatment studies, the adherence of methodology to the contemporary consensus of ideal PE drug trial design, the impact of methodology on treatment outcomes, and the role of PDE-5 inhibitors in the treatment of PE. These studies cover a total of 1102 subjects suffering from PE and treated with sildenafil, tadalafil, vardenafil, either as monotherapy or in combination with SSRIs, clomipramine, or topical anesthetics.

Most of these studies support a role for PDE-5 inhibitors in the treatment of PE and speculate multiple mechanisms,
including a central effect involving increased NO and reduced sympathetic tone, smooth muscle dilatation of the vas deferens and seminal vesicles, which may oppose sympathetic vasoconstriction and delay ejaculation, reduced performance anxiety as a result of better erections, and down-regulation of the erectile threshold to a lower level of arousal so that increased levels of arousal are required to achieve the ejaculation threshold.

The small number of publications and the lack of sufficient data preclude any meta-analysis of results. However, examination of the methodology of these studies, the adherence of methodology to the contemporary consensus of ideal clinical trial design, and the impact of study methodology on treatment outcomes fails to provide any robust empirical evidence to support a role of PDE-5 inhibitors in the treatment of PE, with the exception of men with PE and comorbid ED. Of the 14 studies reviewed, only one fulfilled these criteria and this study failed to confirm any significant treatment effect on IELT.

Caution should be exercised in interpreting data from inadequately designed studies of PDE-5 inhibitors and on-demand SSRI treatment, and their results must be regarded as unreliable. The extremely broad range of IELT fold increases reported with sildenafil (2.7–15.0, mean 6.6), combined sildenafil and on-demand sertraline (3.3–10.0, mean 6.9), and combined sildenafil and on-demand paroxetine (6.6–14.9, mean 10.7) in this systematic review is testament to the unreliability of inadequate study design. In contrast to these findings, the range of placebo IELT fold-increases was relatively narrow (IELT-range 1.2–1.6, mean 1.4) and was identical to the mean 1.4 IELT fold-increase reported in a meta-analysis of other PE drug studies.

Treatment of premature ejaculation and comorbid erectile dysfunction

There is evidence to suggest that PDE-5 inhibitors alone or in combination with an SSRI may have a role in the management of acquired PE in men with comorbid ED. This systematic review includes three studies of patients with PE with comorbid ED treated with a PDE-5 inhibitor alone or in combination with sertraline. In 45 men with PE and comorbid ED treated with flexible doses of sildenafil (50–100mg) for periods of 1–3 months, Li et al. reported improved erectile function in 40 (89%) and reduced severity of PE in 27 (60%).

Improved erectile function was reported by all of the 27 men with reduced severity of PE, of whom 81.5% described themselves as satisfied or very satisfied. Contrary to these findings, only 1 of the 18 men (5.6%) who did not obtain improvement of PE reported treatment satisfaction.

In a group of 37 men with primary or acquired PE and a baseline score from the erectie function domain of the International Index of Erectile Function (IIEF) of 20.9 (consistent with mild ED), Sommer et al. reported a 9.7-fold IELT increase and normalization of erectile function (score of 26.9) with vardenafil treatment as opposed to a 4.4-fold IELT increase with on-demand sertraline. The high level of correlation between improved erectile function with sildenafil and reduced severity of PE reported by Li et al. and the superior IELT fold-increase observed with vardenafil by Sommer et al. indicates that reduced PE severity related to PDE-5 inhibitor use is due to improved erectile function. The IELT fold increase observed by Sommer et al. with on-demand sertraline (4.4) is less than that reported in reviewed studies on men with normal erectile function (mean 5.57, range 3.0–8.5). suggesting that men with PE and comorbid ED are less responsive to on-demand SSRIs and are best managed with a PDE-5 inhibitor alone or in combination with an SSRI. Furthermore, the report of Chia that the addition of sertraline to sildenafil in the treatment of men with ED with comorbid PE was associated with a lesser IELT fold increase (3.3) and lower levels of treatment satisfaction than that seen in men with lifelong PE and normal erectile function treated with on-demand sertraline, suggests that this group of men are less responsive to pharmacotherapy.

The proposed mechanism of action of PDE-5 inhibitors as monotherapy or in combination with a SSRI in the treatment of acquired PE in men with comorbid ED includes the ability to maintain an erection following ejaculation, reduction of the erectile refractory period, and reliance upon a second and more controlled ejaculation during a subsequent episode of intercourse, and a reduction in performance anxiety due to better erections or down-regulation of the erectile threshold to a lower level of arousal so that increased levels of arousal are required to achieve the ejaculation threshold.

The future of drug development

Several in vitro and animal studies have demonstrated that the desensitization of 5-HT-1A receptors, increased activation of postsynaptic 5-HT-2C receptors, and the resultant higher increase in synaptic 5-HT neurotransmission seen with daily dosing of SSRIs can be acutely achieved by blockade of these receptors by administration of an on-demand SSRI and a 5-HT-1A receptor antagonist.

An increasing number of studies report the involvement of central oxytocinergic neurotransmission in the ejaculatory process. In human males, plasma oxytocin levels are elevated during penile erection and at the time of orgasm. Electrical stimulation of the dorsal penile nerve produced excitation in about half of the oxytocin cells in the paraventricular nucleus and supraoptic nucleus of rats. In a rat model, systematic administration of oxytocin facilitated ejaculation by reducing the number of intromissions required for ejaculation, ejaculation latencies, and post-ejaculation intervals. The use of oxytocin receptor antagonists may also have a role but there have been no reports of their efficacy in the treatment of PE.

Drug combinations of on-demand rapid-acting SSRIs and 5-HT-1A receptor antagonists or oxytocin receptor antagonists, or single agents that target multiple receptors, may form the foundation of more effective future on-demand medication.

Surgery

Several authors have reported the use of surgically induced penile hypoesthesia via selective dorsal nerve neurotomy or augmentation of the glans penis with hyaluronic acid gel in
the treatment of lifelong PE that is refractory to behavioral and pharmacological treatment. The role of surgery in the management of PE remains unclear until the results of further studies have been reported.

**Office management of premature ejaculation**

Men with PE should be evaluated with a detailed medical and sexual history, a physical examination, and appropriate investigations to establish the true presenting complaint and to identify obvious biological causes such as genital or lower urinary tract infection (Figure 62.5).

Men with PE secondary to ED, other sexual dysfunction, or genitourinary infection should receive appropriate etiology-specific treatment. Men with lifelong PE should be initially managed with pharmacotherapy. Men with significant contributing psychogenic or relationship factors may benefit from concomitant behavioral therapy. Men with PE secondary to ED can be treated with either ED-specific pharmacotherapy (e.g. PDE-5 inhibitors as monotherapy) or combination therapy with PE-specific pharmacotherapy (e.g. daily or on-demand SSRIs). Recurrence of PE is highly likely to occur following withdrawal of treatment. Men with acquired PE can be treated with pharmacotherapy or behavioral therapy (or both) according to patient and partner preference. Restoration of ejaculatory control in men with acquired PE is likely to occur following completion of treatment but is the exception in men with lifelong PE. Behavioral therapy may augment pharmacotherapy to enhance relapse prevention.

Men with natural variable PE and PE-like ejaculatory dysfunction should be managed with psychoeducation, reassurance, or psychotherapy and should not, in general, be treated with pharmacotherapy.

**Summary**

Recent epidemiological and observational research has provided new insights into PE and the associated negative psychosocial effects of this dysfunction. Recent normative data suggest that men with an IELT of less than 1 minute have ‘definite’ PE, while men with IELTs between 1 and 1.5 minutes have ‘probable’ PE. Although there is insufficient empirical evidence to identify the etiology of PE, there is limited correlational evidence to suggest that men with PE have high levels of sexual anxiety and altered sensitivity of central 5-HT receptors.

The off-label use of SSRIs and clomipramine, along with the development of new on-demand drugs for the treatment of PE, has drawn new attention to this common and often ignored sexual problem. Daily administration of an SSRI is associated with superior fold increases in IELT compared with on-demand administration of SSRIs, including dapoxetine, owing to greatly enhanced 5-HT neurotransmission resulting from several adaptive processes, which may include presynaptic 5-HT-1A and 5-HT-1B or -1D receptor desensitization. However, until the neurobiological, physiological, and psychological mechanisms responsible for PE are better understood, the use of SSRIs or clomipramine for the treatment of PE is not recommended.

![Figure 62.6 Algorithm for the office management of premature ejaculation. SSRI, selective serotonin reuptake inhibitor.](image-url)
understood, ideal treatment outcomes may remain elusive. Drug treatment fails to address directly the causal psychological or relationship factors, and data are either lacking or scarce on the efficacy of combined psychosexual counseling and pharmacological treatment, and on the maintenance of improved ejaculatory control after drug withdrawal. Drug combinations or single agents that target multiple 5-HT receptors may represent the next stage of PE drug development.

Dry ejaculation

Dry ejaculation is a relatively common complaint in older men. It can be due to either retrograde ejaculation or true failure of emission.

Retrograde ejaculation

Retrograde ejaculation is due to incompetence of the bladder neck mechanism most often following transurethral resection of the prostate or open prostatectomy (Table 62.2). These men may have some antegrade ejaculation and usually experience orgasmic sensation. This may, however, be reduced as part of the changes that occur in the male sexual response as a man ages. Retrograde ejaculation and failure of emission can be distinguished by examination of a post-masturbatory specimen of urine for the presence of spermatozoa and fructose. The finding of >5–10 sperm per high-power field in a post ejaculation urine specimen confirms the presence of retrograde ejaculation. In patients with low-volume ejaculate, the finding of more sperm in the urine than in the antegrade ejaculate indicates a significant component of retrograde ejaculation.172

### Table 62.2 Causes of retrograde ejaculation, delayed ejaculation, anejaculation, and anorgasmia

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</table>

### Treatment

Retrograde ejaculation can be surgically treated with bladder neck reconstruction but results remain consistently poor.173 Drug treatment is the most promising approach. As mentioned earlier, alpha-adrenergic sympathetic nerves mediate both bladder neck closure and emission. Several sympathomimetic agents have been described as useful, with mixed results.174 These drugs include pseudoephedrine and ephedrine, and phenylpropanolamine. These agents work by stimulating the release of norepinephrine from the nerve axon terminals but may also directly stimulate both alpha- and beta-adrenergic receptors. The most useful is pseudoephedrine, which is administered at a dose of 120mg 2–2.5 hours before intercourse. The tricyclic antidepressant imipramine, which blocks the reuptake of norepinephrine by the axon from the synaptic cleft, is also occasionally useful.175 The usual dose is 25mg twice daily. Current feeling is that long-term treatment with imipramine is likely to be more effective.

Whilst medical treatment may not always produce normal ejaculation it may result in some prograde ejaculation. In patients who do not achieve antegrade ejaculation with either surgery or medication, sperm retrieval and artificial insemination is an alternative approach. The basic method of sperm retrieval involves recovery of urine by either catheter or voiding after masturbation, and then centrifugation and isolation of the sperm.

### Failure of emission

Any medical disease or surgical procedure that interferes with the sympathetic nerve supply to the vas and bladder neck, the somatic efferent nerve supply to the pelvic floor, or the somatic afferent nerve supply to the penis can result in failed emission or retarded ejaculation. Causes include spinal trauma, especially above the level of T10; the functional sympathectomy that can result from diabetic autonomic neuropathy and surgical sympathectomies following a colectomy, proctectomy, bilateral sympathectomy, abdominal aortic aneurysmectomy and other vascular surgical procedures; open prostatectomy; and retroperitoneal lymph node dissections for testicular tumors (see Table 62.2). Ejaculatory dysfunction following retroperitoneal lymph node dissections is a major concern since it is a procedure usually performed on young men in the prime of their reproductive years. Fossa et al., however, suggest that the use of a modified unilateral node dissection in patients with Stage A tumors lowers the incidence of postoperative ejaculatory disturbance without interfering with the excellent survival rates associated with standard treatment.176 The progressive loss of the fast conducting peripheral sensory axons, which begins to be apparent in the third decade of life, and the dermal atrophy, myelin collagen infiltration,
and pacinian corpuscle degeneration observed in older men, may result in a degree of age-related degenerative penile hyposthesia and difficulty in achieving the ejaculatory threshold.\textsuperscript{177} This is anecdotally exaggerated in men with ED treated with intracavernous pharmacotherapy and is often compounded by the loss of pelvic floor muscle tone seen in the similarly aged, postmenopausal, and often multiparous sexual partners of these men. Certain medications can result in a type of ‘chemical sympathectomy’; included in this category are methyldopa and thiazide diuretics.

Whilst retrograde ejaculation can be surgically treated with bladder neck reconstruction, no surgical procedure exists for the treatment of failed emission. As is the case with retrograde ejaculation, drug treatment is the most promising approach. Whilst medical treatment may not always produce normal ejaculation, it may convert a patient with lack of emission into one with retrograde ejaculation and may result in small amounts of viable sperm, both of which can be combined with standard artificial insemination techniques to produce a pregnancy.

**Inhibited ejaculation**

Inhibited ejaculation is the psychogenic variant of retarded ejaculation, also called ejaculatory incompetence by Masters and Johnson.\textsuperscript{177} It may be defined as ‘recurrent and persistent inhibition of the ejaculation’ as manifested by delay in or absence of ejaculation following an adequate phase of sexual excitement. It may range in severity from very severe, in which a man has never been able to experience waking climax even with masturbation, to milder forms, in which intravaginal climax occurs but only after prolonged thrusting. Clinically it is the least common sexual disorder and it most often presents as a primary disorder. In most cases, however, the problem is situational. Orgasm occurs readily with masturbation but not during intercourse.

Usually only the rare global case of retarded ejaculation presents any difficulty with differential diagnosis. Secondary retarded ejaculation, when it is situational, strongly suggests a problematic relationship. Global secondary retarded ejaculation suggests the development of some psychophysologic or pharmacologic cause, such as sedative hypnotic abuse, narcotic abuse, or alcohol abuse. In very rare instances neurologic disease or neurologic trauma may account for this disorder.

The prevailing wisdom holds that inhibited ejaculation is analogous to female anorgasmia. According to this theory, psychogenically mediated reflex inhibition occurs despite high levels of sexual tension. Apfelbaum has proposed, however, that the disorder is best understood as the surface manifestation of an underlying disorder of sexual desire.\textsuperscript{179} He has theorized that these patients, though they have erections, never pass from initial penile engorgement to the plateau level with high levels of sexual tension. There are patients who typify both of the above perspectives but Martin believes that the majority of patients do reach plateau at some point during thrusting only to experience reflex inhibition and subsequently subside back to pre-plateau levels of tension.\textsuperscript{179} A wide variety of psychologic factors may be responsible for the inhibition, including fear of impregnating the partner, religion, guilt, depressed or repressed hostility towards the partner, oedipal fears of retaliation, and fears of soiling or of defiling the partner with semen.

**Treatment**

As a rule, treatment of inhibited ejaculation with behavioral sex therapy tends to be less successful for orgasm inhibition than for other sexual disorders. The basic treatment strategy requires that the man move by the method of successive approximation from extravaginal ejaculation to ejaculation in the vagina. A treatment sequence might involve a progression from solitary masturbation to masturbation with his wife in the next room, to masturbation in her presence but with her back turned, to masturbation with her looking on, to wife-assisted masturbation to orgasm. Once he has traversed these steps with successful ejaculatory outcome, the patient is asked to insert his penis into the lubricated vagina just at the point of ejaculatory inevitability. After several repetitions of this maneuver, which is designed to desensitize the man to the anxiety associated with intravaginal orgasm, he is asked to insert at plateau, but before ejaculatory inevitability. If he can proceed to ejaculation he is given permission to insert yet earlier in the sexual response cycle. The couple is encouraged to do everything possible to enhance the erotic aspects of the sexual experience and the wife is taught how to cup her husband’s testicles for an extra sensation when he is at high levels of erotic tension. Liberal use of fantasy is encouraged, as is the use of commercially available erotica. It is particularly important that the man not attempt insertion until he has reached high levels of erotic tension during sex play.

**Drug treatment of delayed ejaculation and anejaculation**

There are multiple reports in the literature of the use of a variety of drugs in the treatment of delayed ejaculation or anejaculation. The drugs facilitate ejaculation by either a central dopaminergic or anti-serotoninergic mechanism of action. There are no published placebo-controlled studies and most reports are anecdotal case reports or series that deal with the treatment of SSRI-induced ejaculatory dysfunction.

**Serotonin receptor antagonists**

Several authors have reported that the cerebral serotoninergic system exerts an inhibitory role on ejaculation and male sexual activity in the rat model and that the dopaminergic system, particularly in the anterior hypothalamus, has a facilitatory role.\textsuperscript{180,181} The ejaculatory dysfunction commonly associated with the antihypertensive alpha-methyldopa, which reduces cerebral monoamine levels by suppressing the cerebral dopaminergic system, is consistent with these reports.\textsuperscript{182} The occurrence of paradoxical hypersexuality (e.g. spontaneous orgasm) with clomipramine and fluoxetine, however, suggests that this balance is more complex and that different 5-HT receptor subtypes may have opposing effects on sexual function.\textsuperscript{183,184}

The antihistamine cyproheptadine, which increases cerebral 5-HT levels, has been shown to increase male sexual activity in the rat.\textsuperscript{180} The literature contains several anecdotal
case reports and other small case series of the use of cyproheptadine to reverse the anorgasmia induced by the SSRI antidepressants but contains no controlled studies.185–187 These studies suggest an effective dose range of 2–16mg and administration on a chronic or on-demand basis. McCormick reported the use of cyproheptadine to reverse the anorgasmia induced by the SSRI fluoxetine in two patients.188 Ashton et al. also reported improvement in 12 of 25 men with SSRI-induced sexual dysfunction with a mean dose of 8.6mg, with efficacy limited by sedation and potential reversal of antidepressant effect.186 My experience suggests a role for cyproheptadine in the treatment of both retarded ejaculation and anejaculation, which is limited to a degree by its sedative effect.

Dopamine agonists

Central dopamine activity can be increased by a variety of mechanisms, ranging from the provision of dopamine synthesis precursors (e.g. l-dopa) to the use of substitute neurotransmitters to stimulate central dopamine receptors directly. Amantadine, an indirect stimulant of dopaminergic nerves both centrally and peripherally, which is used in the treatment of Parkinson’s disease and has a limited role as an antiviral agent, has been reported to stimulate sexual behavior, ejaculation, and other sexual reflexes in rats.191,192 Several authors have reported a place for amantadine in the reversal of SSRI-induced anorgasmia.186,193–197 Ashton et al. reported improvement in SSRI-induced sexual dysfunction in 8 of 19 men with a mean dose of 200 mg.186 Balon reported some efficacy with on-demand amantadine 100 mg administered 5–6 hours before coitus in a similar group of patients.193

Several authors have reported induction of ‘PE’ in rats following administration of apomorphine, a central and peripheral dopamine-2 receptor agonist, at a dose of 50 µg/kg. Dopamine receptor antagonists block this effect.198,199 A potential role for apomorphine in the management of ED was first highlighted by Segraves et al.,200 and more recently Heaton et al.,201 have reported an efficacy in excess of 50% with apomorphine in patients with psychogenic ED when it is administered sublingually. Adverse effects of nausea, vomiting, and dizziness are minimized with this sublingual route of administration.

Quininelorane is a highly selective, potent dopamine-2 agonist that was extensively studied in animals in the early part of this decade. Foreman and Hall observed increased mounting, intromission, and ejaculation in both sexually inactive and sluggish rats following administration of quininelorane.202 Prior administration of a dopamine antagonist eliminated these stimulatory effects confirming that these sexual effects were due to stimulation of dopamine receptors. They reported that many rats failed to ejaculate at the extremes of doses, with low doses causing sedation and high doses causing hyperactive behavior such as chewing or snifiting. Animals appear to become more sensitive to dopamine agonists with increased use, suggesting that abuse may eliminate any sexual benefits. Eaton et al. injected quininelorane directly into the rat paraventricular nucleus and MPOA and reported different response with different doses.203 At extremes, quininelorane could cause paradoxical PE, reduced sexual desire, and ED. The reduced sexual response observed at low doses is due to stimulation of dopamine ‘auto-receptors’, which decrease dopamine activity and respond to lower doses than do the stimulatory dopamine-2 receptors. In theoretical clinical use, lowering the dose to avoid excess excitement may result in worse sexual dysfunction than existed before treatment. Human double-blind, placebo-controlled clinical studies of quininelorane were commenced in the late 1980s. They took place at multiple sites and involved more than 500 men and women with ED, reduced sexual desire, and reduced arousal. The US Food and Drug Administration review of the trial data was inconclusive and concern was expressed over the >50% incidence of nausea and hypotension and the indirect negative sexual adverse effects. Clinical studies were terminated and the results remain confidential and unpublished.

Yohimbine

Several authors have reported their experience with yohimbine, a derivative of the bark of the yonoc tree, in the management of SSRI-induced sexual dysfunction.204–206 Yohimbine is an alpha-2 antagonist, an alpha-1-adrenoceptor antagonist, and a calcium-channel blocker. It inhibits platelet aggregation. Price and Grunhaus reported reversal of clomipramine-induced anorgasmia with a dose of 10mg administered 90 minutes prior to coitus.204 In a placebo-controlled study of 15 patients with fluoxetine-induced anorgasmia, Jacobsen reported a 73% response rate to yohimbine.205 Holland reported yohimbine reversal of anejaculation in five of six men with intercourse or masturbation (or both).206 The response to yohimbine is typically delayed, taking up to 8 weeks, and is often associated with adverse effects including nausea, headache, dizziness, and anxiety. Careful dose titration is important since the extremes of dose have less pro-sexual effect.

5-hydroxytryptamine-1A receptor agonists

Buspirone is a benzodiazepine class anxiolytic that possesses 5-HT-1A receptor agonist activity.207 Othmer et al. reported normalization of sexual function in 8 of 10 men with a generalized anxiety disorder and associated sexual dysfunction using a dose range of 15–60mg daily.208 Bupropion is a novel antidepressant that prolongs the action of dopamine by reducing its uptake from the synaptic cleft.209 Ashton and Rosen described reversal of SSRI-induced anorgasmia in 66% of patients studied. An improvement in sexual function was noted by Rowland in 14 non-depressed diabetic men with ED with on-demand doses of 75–150mg.210

Mianserin

Aizenberg et al. examined the effect of the 5-HT-2a–2c and alpha-2-receptor antagonist mianserin in the treatment of patients with sexual dysfunction induced by SSRIs.211 Nine of the 15 subjects reported a marked improvement in their sexual functioning in the areas of orgasm and satisfaction, usually within the first and second week of mianserin treatment. The authors suggested that co-administration of low-dose mianserin might be an additional option in the treatment of sexual dysfunction induced by SSRIs.
Sperm retrieval
In patients who do not achieve antegrade ejaculation with either surgery or medication, sperm retrieval and artificial insemination is an alternative approach if a pregnancy is required.

Ejaculatory dysfunction in spinal cord injury

The ability to ejaculate is severely impaired by spinal cord injury (SCI). Bors and Comarr highlighted the impact of the level and completeness of SCI on the post-injury erectile and ejaculatory capacity (Table 62.3). Unlike erectile capacity, the ability to ejaculate increases with descending levels of spinal injury. Less than 5% of patients with complete upper motor neuron lesions retain the ability to ejaculate. Ejaculation rates are higher (15%) in patients with both a lower motor neuron lesion and an intact thoracolumbar sympathetic outflow. Approximately 22% of patients with an incomplete upper motor neuron lesion and almost all men with incomplete lower motor neuron lesions will retain the ability to ejaculate. In those patients who are capable of successful ejaculation, the sensation of orgasm may be absent and retrograde ejaculation often occurs.

Several techniques for obtaining semen from SCI men with ejaculatory dysfunction have been reported. The intrathecal administration of the anticholinesterase inhibitor neostigmine and the subcutaneous administration of physostigmine to induce ejaculation is more of historical interest and is no longer used, owing to a 60% risk of autonomic dysreflexia, especially in men with injuries above the T5 level. The use of electro-ejaculation to obtain semen by electrical stimulation of efferent sympathetic fibers of the hypogastric plexus is an effective and safe method of obtaining semen. Brindley reported that 71% of men with spinal cord injury who underwent electro-ejaculation achieved ejaculation. Ohl et al.

reported that sperm density and motility were higher in those with incomplete lesions.

Vibratory stimulation is successful in obtaining semen in up to 70% of men with SCI. This technique induces a reflexogenic ejaculation via the sacral roots and the ejaculatory co-ordination center in the upper thoracolumbar spinal cord. It is, however, associated with a significantly higher risk of autonomic dysreflexia than electro-ejaculation. Pre-treatment with a fast-acting vasodilator such as nifedipine will minimize the risk of severe hypertension should autonomic dysreflexia occur with either form of treatment. Percutaneous aspiration of semen from the vas deferens has also been reported as a means of harvesting semen for use with artificial reproductive techniques.

Semen collected from men with SCI is often initially senescent and of poor quality, with a low sperm count and reduced sperm motility, but it may improve with subsequent ejaculations. This poor semen quality may be due to chronic urinary tract infection, sperm contamination with urine, chronic use of various medications, elevated scrotal temperature caused by prolonged sitting, and stasis of prostatic fluid. Testicular biopsies in men with SCI demonstrate a wide range of testicular dysfunction, including hypospermatogenesis, maturation arrest, atrophy of seminiferous tubules, germinal cell hypoplasia, interstitial fibrosis, and Leydig cell hyperplasia. In addition, prostatitis secondary to prolonged catheterization, epididymitis, and epididymo-orchitis can precipitate obstructive ductal lesions and testicular damage.

Painful ejaculation

Painful ejaculation can be caused by any acute genitourinary infection, particularly acute prostatitis or seminal vesiculitis. It may also have a psychogenic basis. The former can be treated with antibiotics, non-steroidal anti-inflammatory agents, prostatic decongestants such as bromhexine, and, if indicated, prostate massage. The latter can be treated by sex therapy.

REFERENCES


Table 62.3 Correlation of erection, ejaculation, and intercourse with level and severity of spinal cord injury

<table>
<thead>
<tr>
<th>Cord lesion</th>
<th>Reflexogenic erections (%)</th>
<th>Psychogenic erections (%)</th>
<th>Successful coitus (%)</th>
<th>Ejaculation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper motor neuron</td>
<td>Complete 92</td>
<td>9</td>
<td>66</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Incomplete 93</td>
<td>48</td>
<td>86</td>
<td>22</td>
</tr>
<tr>
<td>Lower motor neuron</td>
<td>Complete 0</td>
<td>24</td>
<td>33</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Incomplete 0</td>
<td>1</td>
<td>100</td>
<td>100</td>
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</tbody>
</table>


87. Althof SE, Corty EW. Pentech Ejaculation Inventory (personal communication, 2000).


Introduction

Premature ejaculation (PE) or rapid or early ejaculation is generally regarded as one of the most common male sexual problems, with an incidence of 20–30%. Some have suggested a prevalence as high as 75%, although the actual incidence of PE depends on how PE is defined.

Numerous definitions of PE exist, but one of the most commonly accepted is that from the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), which defines PE as 'the persistent or recurrent onset of orgasm and ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the person wishes it'. This definition is a subjective one and does not seek to quantify ejaculatory latency. In practice the intravaginal ejaculatory latency time (IELT), measured with a stopwatch, is commonly used as a way of quantifying PE and treatment success, and also as a standardized way of comparing treatments in clinical research. Considerable variation exists as to where the threshold IELT should be set to define PE, although the consensus of opinion seems to be that men with PE tend to have an IELT of 1–2 minutes or less.7,9

However, the impact that PE has on quality of life is significant, with a similar qualitative impact on the sufferer as erectile dysfunction. Consequently, there is now general agreement that although IELT comparisons are valuable, the evaluation of treatments in well-designed clinical trials should include measures of sexual satisfaction (by the man and his partner), and perception of control over ejaculation, in addition to IELT.8,11

PE is a self-diagnosed condition and most men with the condition do not seek treatment, for reasons of embarrassment, shame, or the belief that no effective treatment exists, but they may try self-help techniques or self-medication: In a large multi-country survey of more than 11,500 men in the USA, Italy, and Germany, fewer than 12% of men who self-reported PE had sought treatment. In a small survey involving in-depth interviews with 28 men with self-diagnosed PE, 89% had tried some form of treatment (including behavioral therapies, pharmaceutical agents, over-the-counter remedies, herbal remedies, creams, and condoms), regardless of whether or not they had consulted a healthcare professional. Such a high figure indicates that men experiencing PE are highly motivated to seek a solution or treatment.

Considering that the frequency of sexual intercourse is highly variable, and spontaneity in sexual intercourse is usually an important factor, the ideal treatment for PE would have the following characteristics; it would:

- be discreet;
- be an 'on-demand' therapy;
- have rapid action;
- be effective from the first dose;
- have high efficacy on IELT and patient-reported outcomes;
- have a low incidence of side-effects; and
- have no unwanted effect on the partner.

It has also been suggested that medication could be used to restore confidence together with behavioral treatment, where available, to help men to learn to overcome PE on their own. PE is of course not a life-threatening condition; therefore safety should be a primary consideration when deciding on a course of treatment.

Current approaches to treatment

There are a range of treatment options for men with PE, directed at different components of the complex mechanism of the ejaculatory process. These include behavioral therapy, systemic treatments, and topical therapies. However, there are currently no pharmacological agents approved for use in PE, and all drugs have to be administered off-label.

Current recommendations from the American Urological Association (AUA) and the second International Consultation on Sexual Dysfunctions (ICSD) recognize that PE is a self-reported diagnosis and emphasize the importance of obtaining a comprehensive sexual history when making a diagnosis; no laboratory or physiological tests are usually required. It is recommended that clinicians also determine if there is concomitant ED and, if present, it should be treated first. The management algorithm for PE produced by the ICSD recommends pharmacotherapy with a selective serotonin reuptake inhibitor (SSRI) or topical anesthetics as the first-line treatment in patients with lifelong PE and as second-line treatment in patients with acquired PE. In reality, pharmacotherapy is likely to be used first-line in both cases, owing to the limited availability of skilled sex therapists and relationship counselors.
such therapies can be useful for some couples, they are rarely successful in the long term since most post-therapy benefits are lost within 3 years of treatment without regular follow-up therapies. In addition, the high cost and limited availability of sex therapists means that this approach is not always practical and indeed is not suitable for men without a steady and supportive sexual partner.

**Behavioral therapy**

Behavioral therapies for PE (such as the ‘stop–start’ and ‘squeeze’ techniques) require a high level of commitment and the involvement of the man’s sexual partner. Although

**Systemic therapy**

The AUA currently recommends three drug treatment strategies to treat PE:

1. Daily treatment with serotonergic antidepressants
2. As-needed treatment with serotonergic antidepressants
Delayed ejaculation is a common side-effect of many psychotropic or antidepressant drugs, in particular of the serotonergic tricyclic antidepressant clomipramine and the SSRIs fluoxetine, paroxetine, and sertraline.\(^{13,19,20}\) These drugs, which are primarily indicated for the treatment of depression, can increase the level of serotonin in the brain, inhibiting the ejaculatory reflex center, and they can prolong IELT for several minutes.

Dosing levels of SSRIs are generally lower for PE than for depression, and various dosing regimens have been tested (including continuous, daily, or situational). Despite this the adverse-event profile appears to be similar; adverse events include dry mouth, drowsiness, nausea, and reduced libido.\(^{21}\) There is also the potential for development of a serious drug interaction that can lead to serotonergic syndrome, which manifests itself as headache, nausea, sweating, and dizziness in mild cases and as hyperthermia, rigidity, and delirium in severe cases.\(^{21}\) Many physicians may consider the side-effects hard to justify for the treatment of PE, in which the primary outcome is patient satisfaction, although the AUA has suggested that the level of adverse events is acceptable for the benefit derived by the patient with PE, and the type and rate of occurrence of side-effects also appears to be acceptable to most patients.\(^{30}\)

Dapoxetine, a novel SSRI, is the first oral agent specifically developed for the management of PE and it has been shown to be effective, well tolerated, and suitable for on-demand use.\(^{22}\) Further research with this drug continues despite the US Food and Drug Administration’s non-approval of dapoxetine for the treatment of PE in 2005.\(^{21}\)

Rationale for the use of topical treatment

There are a variety of theories concerning the etiology of PE.\(^{8}\) Historically, PE was considered a learned behavior and, as a result, behavioral therapy was the standard treatment. However, it is now generally accepted that both biological and psychological factors are important in the etiology of PE. Men with PE appear to have a heightened sensory response to penile stimulation, with a vibration threshold significantly lower than that of normal men.\(^{24,25}\) They also generally exhibit other abnormal autonomic reflex pathways for the ejaculatory process, including shorter bulbocavernous latency time, and higher bulbocavernous evoked potentials.\(^{25,27}\) Considering these sensory differences in men with PE, agents that selectively produce some degree of penile desensitization or act within the afferent–efferent reflex should be effective therapy for PE. Thus, reducing the sensitivity of the glans penis with topical desensitizing agents (such as local anesthetics) should delay ejaculatory latency without adversely affecting the sensation of ejaculation.

Current status of topical treatments

As described above there is currently no approved pharmacological therapy for PE and this has led to the use of over-the-counter remedies and the ‘off-label’ use of local anesthetics. However, there are also novel desensitizing agents specifically designed to treat PE in development.

Compared with orally delivered treatments for PE, topical treatments are appealing in that they can be applied on an as-needed basis and because systemic side-effects are likely to be minimal. However, the application of a desensitizing agent to the penis does have the potential for some degree of penile hypoesthesia and theoretically, transvaginal contamination and female genital hypoesthesia as side-effects.

An important consideration for physician and patient, in this era of evidence-based medicine, is whether there is adequate supportive clinical data for the use of these off-label and novel topical agents. The efficacy and adverse-events profiles for topical treatments, where available, are discussed in the following sections, and comparative data are presented in Table 63.1.

Over-the-counter topical treatments

Lidocaine spray

Lidocaine 9.6% spray, marketed as ‘Studd 100’ or ‘Premjac’, has been available over the counter for over 25 years in some countries and, as their names suggest, these are marketed as products for delaying ejaculation. However the absence of reliable data from clinical trials means that the validity of the claims by the manufacturers cannot be assessed.

Severance secret-cream

Severance secret-cream (SS-cream; Cheil Jedan Corporation, Seoul, Korea), developed at the Yong-Dong Severance Hospital in Korea is made with extracts from nine natural products. Some of these products have local anesthetic as well as vasoactive properties. Several studies using SS-cream on men with PE have been carried out in Korea, but the cream is not approved for use in Europe or the USA and is not legally available outside Korea.

SS-cream is applied to the glans penis 1 hour before intercourse and washed off immediately prior to coitus. Both the latency and amplitude of somatosensory evoked potentials measured at the glans penis were increased over baseline after the application of SS-cream,\(^{28}\) which has also been shown to increase the penile vibratory threshold at the glans penis in a dose-dependent fashion.\(^{29}\) Xin et al. reported significantly prolonged ejaculatory latency in 89.2% of patients treated with SS-cream.\(^{30}\) Adverse effects were noted in 5.9% of patients; these included mild local irritation (local burning or pain) and delayed ejaculation.

The prolongation of IELT has been shown to be dose-dependent,\(^{31}\) with an optimal dose of 0.2g cream. In a multicenter, double-blind study involving 106 patients, the use of 0.2g of SS-cream was reported to increase the mean stop-watch-measured IELT from a baseline of 1.37 minutes to 10.92 minutes, compared with 2.45 minutes with placebo \((p<0.001)\) and was 27 times more effective than placebo in increasing sexual satisfaction \((p<0.001)\). However, almost 19% of episodes of use were associated with mild localized irritation, including pain and burning, and 12 patients reported...
Table 63.1 Comparative efficacy and adverse event data for clinical trials of topical treatments for PE

<table>
<thead>
<tr>
<th>Reference</th>
<th>Treatment</th>
<th>Summary methods</th>
<th>N completing study (mean age or range, years)</th>
<th>Baseline IELT, mean (SD), min</th>
<th>Follow-up IELT mean (SD), min</th>
<th>Satisfaction (man)</th>
<th>AE, incidence – for active treatment</th>
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<tbody>
<tr>
<td><strong>EMLA cream</strong></td>
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<tr>
<td>Berkovitch et al.</td>
<td>2.5 g (pilot study)</td>
<td>Applied to glans penis and penile shaft 30 min before intercourse; covered with condom</td>
<td>11± (36)</td>
<td>ND</td>
<td>ND</td>
<td>5/11 excellent</td>
<td>4/11 better 2 no change±</td>
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<td>1995</td>
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<tr>
<td>Atikeler et al.</td>
<td>2.5 g, (placebo-controlled, dose-finding study)</td>
<td>4 groups × 10 men: 3 applying 2.5 g, covered with condoms and waiting 20, 30 or 45 min, + placebo group</td>
<td>40± (29.4)</td>
<td>&lt;1 min</td>
<td>Placebo 1.0 20 min group 6.71 (2.54) 30 min group 8.7 (1.70) 45 min group loss of erection in all 16/40 = erection loss (numbness) (6/10 in 30 min group 10/10 in 45 min group)</td>
<td>ND</td>
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<td>2002</td>
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<tr>
<td>Busato &amp; Galindo 2004</td>
<td>Double-blind, placebo-controlled</td>
<td>A ‘thin layer’ applied to the glan penis and up to 2 cm of penile shaft; covered with a condom for 10–12 min</td>
<td>29± (completing study)</td>
<td>Placebo 1.67 (0.7) EMLA 1.49 (0.9) Placebo 1.95 (0.12) EMLA 8.45 (0.9) p&lt;0.001 (placebo vs EMLA)</td>
<td>EMLA 11/16 great/excellent±</td>
<td>Men, all, 17% (5/29) Women partners 1/29</td>
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<tr>
<td>TEMPE spray</td>
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<tr>
<td>Henry &amp; Morales 2003</td>
<td>30–50mg (proof of concept)</td>
<td>3–5 sprays (30–50 mg) to glans penis; in situ for 15 min; wipe off before contact with partner</td>
<td>11± (42)</td>
<td>1.4 (1.1)</td>
<td>11.35 (10:72) p=0.008 vs baseline</td>
<td>8/11 better/much better± 7/11 partners better/much better±</td>
<td>Men 3/11 Women 2/11</td>
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<td>2003</td>
<td></td>
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<tr>
<td>Dinsmore et al. 2006</td>
<td>30–50mg (double-blind, placebo-controlled)</td>
<td>3–5 sprays (30–50mg) to glans penis; in situ for 15 min; wipe off before contact with partner</td>
<td>54± TEMPE (38.5) Placebo (39.3)</td>
<td>TEMPE 1.0 (1.2) Placebo 0.9 (0.7) TEMPE 4.9 (4.9) Placebo 1.6 (1.6) p&lt;0.01 vs baseline</td>
<td>Mean change in SQoL points baseline to end of treatment± Men: TEMP 7.0 Placebo 5.5 (p = 0.48) Women TEMP 3.3 Placebo 1.8 (p = 0.56)</td>
<td>Men 4/26 Female 1/26</td>
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## Dyclonine/alprostadil cream

| Study | Comparison of cream formulation; dyclonine 1%, alprostadil 0.4%, dyclonine 0.5%/alprostadil (placebo controlled) | Cream administered to tip of the penis at the meatus 5–10 min before coitus | 30% (28–62) | Not stated | Placebo 2.34 (0.34) | Dyclonine 3.21 (0.31) | Alprostadil 3.75 (0.34) | Dyclonine/alprostadil 4.08 (0.3) | p<0.05 vs placebo | %-answering ‘yes’ to patient satisfaction question in diary Placebo 66.7 | Dyclonine 73.3 | Alprostadil 83.3 | Dyclonine/Alprostadil 86.7 | Placebo 5% | Dyclonine 17.5% | Alprostadil 20% | Dyclonine/Alprostadil 17.5% | All AIs were local and mild to moderate in nature

### SS-cream

| Study | 0.1g | Applied 1 hour before sexual contact and washed off before intercourse | 186% (42.3) | 1.50 (0.58) | 10.89 (5.60) | p<0.001 vs baseline | % Satisfied with treatment
Not satisfied (10.8) Satisfied (89.2%) | Overall 5.9% (11/186) 7/186 mild local irritation 4/186 delayed ejaculation

| Study | 0.05g | 0.10g | 0.15g | 0.20g | (placebo controlled) | Applied 1 hour before sexual contact and washed off before intercourse | 50% (37) | 1.35 (0.07) | SS-cream:
0.05g 4.47 (0.81)
0.10g 5.34 (0.79)
0.15g 6.22 (0.87)
0.20g 11.06 (1.17) | Sexual satisfaction ratio
Placebo 26% SS-cream:
0.05g 60%
0.10g 70%
0.15g 78%
0.20g 90% | All test trials:
14.8% (37/250) mild local burning sensitivity 0.04 (1/250) mild penile pain Reports of mild local burning sensations increased in a dose-dependent fashion

| Study | 0.2g (double-blind, placebo-controlled) | Applied 1 hour before sexual contact and washed off before intercourse | 106% (38.7) | 1.37 (0.12) | Placebo 2.45 (0.29) SS-cream 10.92 (0.95) p<0.001 (between treatments) | Sexual satisfaction ratio
Placebo 19.81% SS-cream 82.19% | All test trials:
14.72% (78/530) mild burning 3.77% (20/530) mild pain Mem 3/106 erectile dysfunction 4/106 delayed ejaculation 5/106 no ejaculation

ND=not done; *Patients with self-diagnosed PE; History of primary or secondary PE not stated; §Satisfaction assessed on a scale of –1 for worse, 0 for no change, 1 for better than usual, 2 for excellent; *Self-diagnosed primary PE; Patients with self-diagnosed primary and secondary PE; %Level of satisfaction defined using a linear scale pf 1–10, as bad (1–4), regular (5,6), good, (7), great (8,9) or excellent (10); Study-specific male and female sexual quality of life questionnaires, each containing 10 statements; †Entry criteria not stated; ‡132 with primary PE and 54 with secondary PE and including 64 patients with PE combined with mild ED; Patients were asked to estimate the degree of satisfaction for both their partners and themselves; †Method of determining sexual satisfaction not stated; §Sexual satisfaction ratios determined by adding the percentage of patients who reported being satisfied (effective) and very satisfied (excellent).
negative sexual side-effects such as delayed ejaculation, anejaculation, and erectile dysfunction.\(^{35}\)

Despite these promising results, SS-cream has an unpleasant smell and color, which makes it unacceptable to many patients. A reformulation has resulted in ‘renewed SS-cream’ (RSSC) which is a new topical agent composed of the two main components of the original SS-Cream; Korean ginseng and Bufonis venenum in a hydrobase and enhancer without smell or color.\(^{33}\) So far, only the results of animal studies have been published. The authors claim that RSSC delays the latencies of the spinal somatosensory evoked potentials in rabbits more effectively than the original SS-cream. However, the ingredient Bufonis venenum, has been shown to produce contact dermatitis\(^{34}\) and the likelihood of this cream gaining regulatory approval outside of Korea appears to be remote.

Off-label topical treatments

**Lidocaine–prilocaine cream**

Separately, lidocaine and prilocaine are crystalline solids. When mixed together in equal quantities by weight, however, they form a liquid eutectic mixture that can be formulated into preparations without the use of a non-aqueous solvent. This allows higher concentrations of anesthetic to be formulated into the preparation and maintained during application. EMLA\(^{2}\) (Eutectic Mixture of Local Anaesthetic; AstraZeneca) is a local anesthetic cream containing 2.5% each of lidocaine and prilocaine for topical application. Developed to anesthetize intact skin, it is available as an over-the-counter product in some countries.

The first pilot study evaluating lidocaine–prilocaine cream for the treatment of PE included 11 subjects.\(^{35}\) The cream (2.5g) was applied to the whole glans and shaft of the penis 30 minutes prior to intercourse and covered with a condom, which could be removed prior to intercourse (and the cream wiped off) if desired. Nine of the 11 patients rated their performance as ‘excellent’ or ‘better’ and all 11 partners were satisfied with the treatment results.\(^{35}\)

In order to determine the optimal time that the anesthetic cream should be on the penis prior to intercourse, Atikeler et al. carried out a placebo-controlled trial with 10 patients in each treatment group, varying the application time from 20–45 minutes, with a condom. In the 20- and 30-minute application groups the IELT increased compared with placebo, but all men in the 45-minute group suffered from penile numbness and loss of erection. The optimal application time was considered to be 20 minutes.\(^{36}\)

The largest double-blind, placebo-controlled clinical trial of lidocaine–prilocaine cream to date involved 42 patients; 21 in each group.\(^{37}\) Patients were asked to apply a thin layer of cream to the glans penis, extending the coverage for up to 2cm on the penile shaft. They were then asked to cover the cream with a condom for 10–20 minutes before intercourse and to use this treatment each time they had intercourse over 30–60 days. The treatment resulted in a 5.6-fold increase in IELT. However, only 29 of the initial 42 participants completed the study. Of the patients completing the study, 11 out of the 16 who responded reported ‘great’ or ‘excellent’ sexual satisfaction. Loss of penile sensation, retarded ejaculation, and penile irritation were a problem for 5 men, and 1 female partner reported decreased vaginal sensitivity.

It can be concluded that lidocaine–prilocaine cream has some degree of efficacy in the treatment of PE but is inconvenient, messy, and slow-acting, and it is not approved for this indication. It also has problems associated with hypoesthesia.

**Novel topical agents in development**

**Dyclonine–alprostadil cream**

Dyclonine, a local anesthetic used most commonly in dentistry, has been combined in a cream formulation with alprostadil (prostaglandin E-1), a vasodilator used in erectile dysfunction (ED), and the combination is under development (NexMed, USA) as a topical treatment for PE. So far only one pilot study has been published (in abstract form) in which creams containing dyclonine alone, alprostadil alone, or a dyclonine–alprostadil combination with two different drug concentrations were compared in a double-blind, crossover trial.\(^{38}\) This pilot study involved 30 patients who applied the cream 5–20 minutes before intercourse. A significant synergistic effect was observed with the cream containing 0.5% dyclonine and 0.4% alprostadil in comparison with the treatment with creams containing 1% dyclonine alone or 0.4% alprostadil alone (p<0.05) (see Table 63.1). Baseline IELTs are unfortunately not reported, but the mean IELT post-dosing were 2.34 minutes and 4.08 minutes in the placebo and dyclonine–alprostadil combination groups, respectively (p<0.05). Adverse events were experienced by 17.5% of men and are described as local and mild to moderate in nature, with an average duration of 18.2 minutes. Details of the adverse events and also whether or not any of the patients’ partners experienced adverse events are also not provided. The most frequently reported adverse events in patients using alprostadil cream to treat erectile dysfunction are application site-related, such as penile burning, genital pain, and genital erythema, mostly resolving within 2 hours.\(^{39}\) The results of further studies using this cream are awaited with interest.

**Prilocaine–lidocaine spray**

TEMPE (Topical Eutectic Mixture for Premature Ejaculation, Pethora Solutions Ltd.) is a proprietary formulation of lidocaine and prilocaine in a metered dose aerosol delivery system specifically designed for use in PE; the system delivers 7.5mg lidocaine base plus 2.5mg prilocaine base per actuation. The mixture is alcohol-free so there is little risk of stinging on application, and although it is oil-free, the mixture forms a clear, slightly oily, odorless solution that remains adherent to the application site. It can easily be wiped off if necessary with a damp cloth, so no condom is required.\(^{40}\)

The metered dose spray delivery system allows the desensitizing agents to be deposited in a dose-controlled, concentrated film on the glans penis, and they can then penetrate the glans within 5–10 minutes.\(^{41}\) The eutectic mixture is slower to penetrate intact keratinized skin and as such is not likely to anesthetize the shaft of the penis or the hands.\(^{41}\)
In the first open-label pilot study, 11 patients reported stopwatch-timed IELTs at baseline and on five subsequent encounters when using the spray 15 minutes before intercourse. The average IELT increased from 1 minute 24 seconds to 11 minutes 21 seconds (p=0.008), representing an average eight-fold increase. In addition, 8 out of 11 patients and 7 out of 11 partners rated their sexual satisfaction as ‘better’ or ‘much better’.

In a recently published phase 2, placebo-controlled trial, 54 patients using the prilocaine–lidocaine spray were able to prolong their IELT from a baseline of 1.0 minute to 4.9 minutes. The treatment was also well tolerated, with only three patients (12%) experiencing hypoaesthesia (numbness of the penis) and a fourth patient experiencing loss of erection; none of the adverse events resulted in treatment discontinuation. The spray was also well tolerated by the female partners, with only one partner experiencing a mild burning sensation during intercourse each time her partner used the spray; again, this did not result in discontinuation.

Discussion

Compared with systemic treatments for PE, topical treatments do offer certain advantages: they can be applied when needed, and systemic side effects are unlikely. However, they do have a number of potential drawbacks: they can be messy, they can interfere with spontaneity, and they can cause numbness in the man or his partner. Dependent on formulation, they also require a period of time between application and maximum effect and need either to be used with a condom or be washed or wiped off before intercourse, which will have an effect on spontaneity and may decrease arousal. The cream formulations (lidocaine–prilocaine, dyclonine–alprostadil, and EMLA®) require a 5–20-minute application and the potential use of a condom, whereas the spray formulation (lidocaine–prilocaine) has 5–15-minute application time and is easy to administer, remaining adherent to the glans penis after application and being less likely to penetrate intact keratinized skin causing anesthesia of the shaft of the penis.41

However, the evaluation and comparison of the outcomes of clinical trials for PE agents remains difficult whilst considerable debate over the definition of PE continues. A critical review of the methodology of studies in PE has revealed the scale of the differences and the resultant difficulties in comparing results from these studies.42 It is therefore important to exercise a degree of caution when comparing headline results. Recommendations for standards for clinical trials in PE3,11,42 include the use of a precise definition of premature ejaculation (e.g. ejaculation that occurs within 1 minute after vaginal penetration in more than 90% of intercourse); a randomized, double-blind, prospective design; the use of validated outcome measures (such as IELT); and the use of a stopwatch at each coitus, both during baseline and during drug treatment. Use of such stringent parameters in all future trials would enable meaningful meta-analyses to be carried out.

In conclusion, the treatments options for men with PE are limited until a safe, efficacious, practical and preferably as-needed agent with a suitable risk–benefit profile is approved.

REFERENCES


Potency-preserving surgery: radical prostatectomy and other pelvic surgery

Paolo Gontero and Roger S Kirby

Introduction

Sexual dysfunction, especially erectile dysfunction (ED), is a well-recognized complication of abdominal and pelvic surgery. Radical procedures for pelvic malignancy, vascular operations, and transurethral prostatic surgery can all lead to erectile and ejaculatory dysfunction. As most of these procedures are performed in middle-aged to elderly patients, there has, in the past, been a tendency to disregard the importance of loss of potency. However, some men now have expectations of unimpaired sexual function well into their seventh or even eighth decades; impotence can, therefore, have a profound effect on their quality of life.

Over the past 20 years, major advances in understanding of the mechanisms leading to erectile dysfunction after surgery have fostered the development of surgical approaches that allow preservation of sexual function. Together with improvements in the treatment of postoperative ED, potency-preserving techniques have significantly improved the outlook for patients undergoing abdominal and pelvic surgery.

Radical prostatectomy

As prostatic carcinoma continues to undergo a real increase in incidence and diagnosis tends to be made at earlier stages than in the past, an increasing number of men are being offered treatment by radical prostatectomy, usually via the retropubic route and lately by laparoscopic means, with or without robotic assistance. Traditionally, impotence was almost inevitable after this procedure; in the early 1980s, however, Patrick Walsh and his colleagues demonstrated that ED after radical prostatectomy was secondary to injury to the branches of the pelvic plexus that innervate the corpora cavernosa. On the basis of their discovery, they proposed alterations in surgical technique to avoid this complication.

Anatomy

Although the importance of the pelvic plexus in erectile processes was well recognized, the branches of the plexus supplying the corpora cavernosa had not been accurately located prior to Walsh’s work. Because the cavernous nerves are of small caliber and lie encased within fibrofatty tissue, they are difficult to dissect in the adult cadaver. Walsh and Donker therefore initially traced their course by dissections in male fetuses and stillborn infants. Their findings were later confirmed in adult cadavers. The pelvic plexus is formed by parasympathetic visceral efferent preganglionic fibers (the nervi erigentes) arising from sacral segments S2, S3, and S4 and from postganglionic sympathetic fibers arising from the thoracolumbar region (T11–L2) and traveling to the plexus via the hypogastric nerve. The parasympathetic fibers control erectile function, while the sympathetic fibers play an important role in ejaculation.

The plexus is situated retroperitoneally in the sagittal plane on the lateral wall of the rectum, 5–11 cm from the anal verge (Figure 64.1). It lies lateral and posterior to the seminal vesicle. Because the plexus is surrounded by thick fascia, the seminal vesicle is a useful intra-operative landmark as its tip is opposite the midpoint of the plexus. The cavernous branches travel from the plexus towards the posterolateral aspect of the base of the prostate in association with the capsular arteries and veins of the prostate. As they gradually coalesce towards the gland, the fibers are running in the lateral pelvic fascia outside the prostatic capsule and outside Denonvillier’s fascia. This arrangement underlies two important anatomical principles: first, the location of the cavernous nerves outside the prostatic capsule and Denonvillier’s fascia means that, if cancers are located entirely within the capsule, preservation of potency should be possible without compromising excision of organ-confined tumors; and secondly, the cavernous nerves are not themselves visible with the naked eye, and their association with the capsular vessels of the prostate to constitute the neurovascular bundle therefore provides a macroscopic landmark for these microscopic nerves. From the apex of the prostate, the nerves run posterolateral to the urethra to penetrate the urogenital diaphragm. The fibers then pass behind the dorsal penile artery and nerve before diverging laterally to enter the corpora cavernosa.

Recently, a slightly different view of the anatomical location of the neurovascular bundles at the prostate level has been proposed. By studying the development of cavernosal nerve fibers in fetuses of different gestational age, Lunaceket al. found that the neurovascular bundles run dorsolateral to the future prostate only in the early gestational phase (up to the
10th week). Thereafter, as the prostate begins to develop, the nerve fibers are displaced more anteriorly, along the convex surface of the prostatic capsule, assuming the shape of a ‘concave curtain’ covering both prostatic lobes. With the development of benign prostatic hyperplasia (BPH) in the adult, the nerves are increasingly displaced laterally and anteriorly. Another finding of the study was that at the membranous urethra the nerve fibers are present all around the urethra between the 3 o’clock and the 9 o’clock positions and not only lateral to the urethra. These new anatomical insights have led to recent refinements in the surgical technique of nerve-sparing radical prostatectomy.

**Surgical technique**

Open radical retropubic prostatectomy

nerve-sparing techniques

Traditional methods of open radical prostatectomy have often relied on blind or blunt dissection. Since the importance of the neurovascular bundle in erectile function was not appreciated, no attempts were made to preserve it. Examination of pathological specimens from non-nerve-sparing prostatectomies reveals no evidence that the bundles were actually resected; instead, it appears that they were inadvertently damaged. The cavernous nerves are particularly vulnerable at several points during the procedure, including apical dissection and transection of the urethra, separation of the prostate from the rectum, and division of the lateral pedicle.3,5,7,8

On the basis of his anatomical studies, Walsh described a new method of radical prostatectomy designed to avoid damage to the cavernous nerves in these areas. His single most important innovation was the application of the neural anatomy described above to facilitate accurate intra-operative identification of the neurovascular bundles. This in turn is critically dependent on a second maneuver – namely, control of blood loss from the dorsal venous complex and Santorini’s plexus, the anatomy of which was also clarified by Walsh et al.9 The nerve-sparing technique involves initial control of bleeding from the dorsal complex followed by transection of the urethra.

This is the first critical point where the bundles may be damaged. Because the neurovascular bundle when approaching the prostatic apex is located underneath the sphincter and can be fixed into a medial position by an apical vessel, care is used to transect only the lateral edges of the sphincter at the urethral level, refraining from any dissection underneath the prostatic apex.10 Subsequently, the dissection of the bundle is carried out starting at the bladder neck and proceeding down to the apex until a groove appears on the posterolateral edge of the prostate that serves as a landmark for the neurovascular bundle, which is located just laterally to it. Following the groove down to the apex will enable the identification of the bundles at the level of the transected urethra: only at this point can the dissection be completed at the apex and carried out posterior to develop the prostatic–rectal plane without damaging the nerves.

The last critical point for a successful nerve-sparing technique is represented by the dissection of the seminal vesicles. Because the midportion of the pelvic plexus is anatomically located at the tip of the seminal vesicles, the dissection of these small organs must be carried out very carefully, particularly in the lateral aspect, where small arterial branches are often encountered and need to be clipped close to the seminal vesicles.

If unilateral neurovascular bundle excision is necessary, it may be possible to preserve the contralateral bundle. When this technique is used, all structures can be visualized and a deliberate decision made as to whether they can be preserved or must be sacrificed for disease control.5

Based on the anatomical findings of a ‘curtain-shaped’ disposition of the neurovascular bundles on the anterolateral surface of the prostatic lobes, other authors6,11 now prefer to start the dissection of the prostatic fasciae more anterior (i.e. at the 1 o’clock and 11 o’clock positions) to preserve all the nerve fibers that are spread concavely in the ‘curtain’.  

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Figure 64.1 Anatomical details of the pelvic plexus as shown in a classic anatomical textbook drawing and in a cadaveric picture.
Endoscopic techniques of nerve-sparing radical prostatectomy

Techniques for nerve preservation during the laparoscopic and the robotic radical prostatectomy are currently available, with preliminary functional outcomes at least as good as those achieved with open surgery.

For the laparoscopic approach, both retrograde and antegrade techniques of nerve preservation have been described. In the former, the periprostatic fascia is initially incised at the apex of the prostate and the neurovascular bundle dissected off. The latter consists of making a ‘lateral’ incision in the periprostatic fascia after dividing the prostatic pedicles and then carrying out the bundles dissection from these lateral incisions. In a recent modified technique – intrafascial nerve-sparing endoscopic extraperitoneal radical prostatectomy – the dissection starts at the bladder neck without incision of the endopelvic fascia. A bilateral sharp incision of the periprostatic fascia is then conducted from the bladder neck down to the apex, and the plane between the prostate and the fascia developed. Only at this point is the endopelvic fascia reflection over the prostate incised.

The main goal of this approach is to develop the right plane and detach the prostate from its ‘envelopment’, leaving intact all lateral enveloping periprostatic fascia (including the endopelvic fascia) and puboprostatic ligaments as a continuous structure.

Similar techniques have been reported for the robotic radical prostatectomy. Above all, the Vattikuti Institute prostatectomy claims promising functional results by sparing the whole periprostatic fascia (named the veil of Aphrodite in view of the peculiar distribution of the cavernosal nerve fibers).

Results of nerve-sparing radical prostatectomy

Tumor excision

It is clearly important that preservation of potency is not achieved at the expense of cancer control. Findings on whole-mount specimens from standard blunt dissection radical retropubic and perineal prostatectomies have therefore been compared with nerve-sparing prostatectomy specimens to determine the effect of the nerve-sparing modification on histology of the surgical margins.

Although perineal prostatectomy tends to remove less periprostatic tissue and skeletal muscle than either of the retropubic techniques, it appears that all of the approaches allow adequate removal of limited prostate cancer. In one series of 100 nerve-sparing radical prostatectomies, capsular penetration was present in 41% of cases but only seven patients had positive surgical margins, all of whom had extensive extraprostatic disease. In no case was the margin positive only at the site of the nerve-sparing modification.

Further studies have also indicated that patients with positive surgical margins tend to have extensive extracapsular disease, often with seminal vesicle or lymph node involvement. It is unlikely that surgery of any type will eradicate these tumors completely. In one series of 459 patients, three patients were identified with positive margins only at the site of the nerve-sparing modification. Although margin positivity might have been avoided by excision of the neurovascular bundle, the number of affected patients is small. Furthermore, the long-term significance of these involved margins remains unclear.

Current wisdom therefore is that the nerve-sparing technique rarely compromises cancer control. Precise identification of the neurovascular bundle with wide excision when necessary may even allow more extensive resection than blunt dissection in selected cases. Several major centers have reported the results of large series of open nerve-sparing radical retropubic prostatectomies since the introduction of the technique.

The supporters of the endoscopic techniques of radical prostatectomy advocate the achievement of better preservation of neurovascular bundles as a result of improved magnification. Indeed, excellent potency rates have been reported particularly with the robotic ‘veil of Aphrodite’ technique.

### Table 64.1 Comparative potency rates and surgical margins with open retropubic and endoscopic radical prostatectomy contemporary series

<table>
<thead>
<tr>
<th>Series</th>
<th>Technique</th>
<th>n</th>
<th>Mean follow-up (months)</th>
<th>Positive SM (%)</th>
<th>Intercourse rate at 1 year (%)</th>
<th>Patients with normal IIEF (%)</th>
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<tr>
<td>Rabhani F et al.</td>
<td>RRP</td>
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<td>56</td>
<td>Minimum 3 months</td>
<td>10.7</td>
<td>NA</td>
<td>66</td>
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</table>

Table 64.1 shows comparative potency rates and surgical margins from open retropubic and endoscopic radical prostatectomy series.

For the open approach, the best results are reported by the originator of the technique and his associates, with overall potency rates of 68% among men potent preoperatively.21 The robotic approach seems to guarantee even better functional results with no additional or even less cost in terms of surgical margins, but data are not yet mature. On the whole, other groups have found potency rates to be somewhat lower. Therefore, although rates of recovery of erectile function are better with than without non-nerve-sparing techniques, the morbidity in terms of sexual function is still considerable. Various factors affect the likelihood of impotence following open radical prostatectomy.

Number of neurovascular bundles spared
The single most important factor in determining preservation of potency is the number of neurovascular bundles injured. Potency rates are reported as 31.9–76% for bilateral nerve-sparing procedures, 13.3–60% for unilateral nerve-sparing procedures, and 0–1.1% for non-nerve-sparing procedures.22,23 On the whole, a 25% reduction in the success of a nerve-sparing procedure has to be expected if only one neurovascular bundle is spared at the time of surgery.24

Stage and tumor volume
Stage and tumor size also influence postoperative potency.22,23,26,27 In one series, a tumor volume of less than 3cm³ and the absence of lymph node or seminal vesicle involvement were associated with preservation of potency.22 However, stage determines the extent of surgery required for tumor excision and therefore the number of neurovascular bundles that can be spared; it is not, therefore, an independent predictor of outcome. For example, in one report, only 9% of patients in whom a bilateral nerve-sparing procedure was possible presented with clinical stage B2 or C disease compared with 51% of those in whom unilateral excision of the neurovascular bundle was required.23

Age
Younger patients tend to fare better in terms of postoperative potency than their older counterparts.22,23,25,26 Men less than 50 years of age tolerate unilateral neurovascular bundle excision with potency rates similar to those of bilateral nerve-sparing procedures (90% potency). In older men, however, excision of one neurovascular bundle significantly reduces the likelihood that potency will be retained.23 The relatively young average age of patients in Walsh’s series may partly explain the excellent overall results achieved in this center.33

Response to sildenafil treatment, a known indicator of a successful nerve preservation following radical prostatectomy, is significantly enhanced in patients less than 65 years compared to those over 65 (63% versus 43%).27

Preoperative sexual activity
Patients who are sexually active before surgery are more likely to recover their potency postoperatively, even allowing for the higher incidence of sexual activity in younger men.22 In the study by Raina et al., a preoperative erectile function domain score of the International Index of Erectile Function (IIEF) below 16 was associated with a reduced probability of postoperative recovery of potency.27

Although impotence after radical prostatectomy is primarily neurogenic in most cases, the existence of patients who do not respond to intracavernosal papaverine postoperatively suggests that vascular injury can also contribute to ED.29 This impression is confirmed by penile Doppler ultrasound studies that reveal evidence of arterial insufficiency in 40% of men after radical prostatectomy.29 The main blood supply to the corpora cavernosa is from the internal pudendal artery, which is not usually ligated during radical prostatectomy. However, it is likely that there are also collateral sources, and it is thought that loss of these collaterals may lead to vasculogenic impotence. Older patients with atherosclerosis of the internal pudendal vessels may be at particular risk. Likely sources of collateral blood supply to the penis include the arterial branches running beneath the anterior capsule of the prostate, which are visible following division of the dorsal complex. These vessels are not amenable to preservation during radical prostatectomy.30

There has also been a great deal of interest in the effect of damage to accessory branches to the internal pudendal artery, which can arise from the obturator and inferior and superior vesical arteries (Figure 64.2). One cadaveric study has suggested that accessory arteries are present in 70% of patients.31 At radical prostatectomy, however, it appears that accessory arteries amenable to preservation are present in only 4% of patients and that preservation has no effect on potency rates.30 It is also important to recognize that, although most impotence after radical prostatectomy has an organic basis, anxiety is common in men receiving treatment for prostate cancer and psychogenic factors may contribute to ED.32

Most patients who regain potency after radical prostatectomy recover within 6–12 months,24 although improvement can continue for up to 2 years postoperatively. Patients who have undergone excision of one neurovascular bundle lag behind those who have a bilateral nerve-sparing operation.23 Although potency rates from several large series are impressive, these data should be interpreted with caution. In the literature, potency is generally defined as the ability to achieve an erection sufficient for vaginal penetration and orgasm. Although patients may fit this description, many notice a definite change in the quality of their erections after surgery, which can be associated with reduced sexual satisfaction.22,25 Koeman et al. found that fewer than half of their patients defined as potent on the basis of erections sufficient for vaginal penetration were satisfied with their erections or achieved intercourse at least once a month.33

Furthermore, potency is only a single aspect of sexual function. Radical prostatectomy may also alter orgasmic sensation, although few studies address this problem. Geary et al. noted that only 10% of patients (regardless of potency) reported decreased orgasmic sensation.22 This is important, in that these patients are likely to respond well to intracavernosal injection therapy, vacuum devices, or penile prostheses. In a study from the Netherlands, however, that was based on a semi-structured interview and a self-administered questionnaire, 80% of men experienced weakened orgasmic sensation.
after surgery. Moreover, 64% suffered involuntary loss of urine at orgasm, although all but one were completely continent at other times; this caused half of these men to avoid sexual contact. Diminished libido was also common.13

The pathophysiology of these changes in orgasmic sensation is poorly understood but may relate to the unavoidable excision of small nerve fibers surrounding the prostate and seminal vesicles. These statistics illustrate two important principles: first, preservation of erections adequate for penetration does not in itself guarantee satisfactory sexual performance in all patients; and secondly, it is becoming clear that, when patients are asked in person about their sexual function, satisfaction rates tend to be lower than those reported by clinicians.23,24 Allowing for these factors, it is probably unrealistic to offer the average prostate cancer patient a greater than 50% chance of retaining preoperative levels of sexual function after radical prostatectomy; however, a proactive approach with an emphasis on penile rehabilitation with phosphodiesterase (PDE) type 5 inhibitors and other techniques can definitely improve outcomes.

Transurethral prostatic surgery

ED is less common following transurethral prostatic surgery but nevertheless affects up to 14% of men undergoing transurethral resection of the prostate (TURP).15 The etiology of post-TURP impotence is not absolutely clear; it is, however, likely that the cavernous nerves and arteries are damaged by perforation of the prostatic capsule, extravasation of irrigant, or injudicious electrocautery of the capsule, particularly at the apices. These events should therefore be avoided if possible. It is also essential to discuss the risk of postoperative impotence with the patient when obtaining informed consent for the procedure. Other techniques, such as Greenlight laser vaporization of the prostate, are claimed to have a lesser impact on erectile function but there are little published comparative data to corroborate that claim.

Radical cystectomy and urethrectomy

In males

ED is a common complication of radical cystoprostatectomy for bladder carcinoma, and the nerve-sparing approach described above can also be applied to this procedure.26 Initially, proponents of the technique have reported potency rates similar to those achieved following radical prostatectomy (71%).27 In a recent series, the five-item version of the IIEF (IIEF-5) was administered to 49 preoperatively potent subjects who had undergone cystoprostatectomy at a median follow-up of 47 months.28 The mean postoperative scores were significantly reduced compared with the preoperative values, with 86% of patients unable to achieve vaginal penetration after surgery. Of note, only 6 out of 16 (37%) patients who had undergone a nerve-sparing procedure had erections sufficient for vaginal penetration.

Understanding of the pelvic neuroanatomy has also been applied to urethrectomy. As described above, the cavernous nerves lie posterolateral to the membranous urethra as they traverse the urogenital diaphragm. Distal to the membranous urethra they diverge laterally into the corpora cavernosa. The nerves are, therefore, most vulnerable during dissection of the membranous urethra. Brendler et al. recommend removing only urethral mucosa and smooth muscle during separation of the urethra from the urogenital diaphragm, preserving as much striated muscle as possible; the neurovascular bundles can then be gently pushed away from the posterolateral aspect of the urethra.29 This technique has allowed preservation of potency in the small number of cases reported.

For accurate nerve preservation during radical cystectomy, Kessler et al. advise neurovascular bundle preservation dorsolateral to the prostate as well as more cranially in the angle between the prostate, bladder and seminal vesicle by ligation and division of the dorsomedial pedicle close to the seminal vesicle.30
With the aim of preserving erectile and ejaculatory function, a modified cystectomy that successfully preserves seminal vesicles and the prosthetic capsule after transurethral resection or that leaves the prostate intact has been reported. Despite the concerns for the oncological control of the disease, excellent results in terms of potency preservation and successful intercourse have been reported with the nerve- and seminal-sparing cystectomy.

In females

Female sexual function relies on the integrity of the female external genitalia (which comprise the labia, the clitoris, and the vestibular bulbs) and the internal genitalia (the vagina, fallopian tubes, uterus, and ovaries). The clitoris is an erectile organ formed by two erectile bodies fused in the midline, similar to the penile cavernosal bodies. During sexual stimulation, increased blood flow causes clitoris engorgement and subsequent lubrication. The same occurs for the vagina, which becomes engorged during sexual stimulation and forms a plasma trasudate that is critical during the sexual arousal phase. The autonomic innervation of the proximal two-thirds of the vagina and clitoris (the equivalent of the male neurovascular bundles) leaves the pelvic plexus and travels within the uterosacral and cardinal ligaments, along with the vessels.

Surgical factors that can affect female sexuality in regard to cystectomy are the preservation of the nerves (located on the lateral walls of the vagina), the preservation of a stump of distal urethra (in order not to devascularize the clitoris), and the technique of vaginal reconstruction. Horenblas et al. conducted a prospective trial of modified cystectomy for normal sexual function and anatomic urinary tract reconstruction without oncological concessions. They managed to preserve clitoral vasculature with the transection of the urethra at the level of the bladder neck and retrograde dissection of the bladder from the anterior vaginal wall. The dissection close to the vaginal wall allows the preservation of both the clitoris and the neurovascular bundle.

Reconstruction of the vagina is achieved by retubularization in a vertical fashion, creating a narrower cylinder or by dissecting the posterior vaginal wall off the rectum to create a flap that is turned downwards to form an adequate vaginal caliber but one of decreased depth. A case series reported by Schover et al. found a higher rate of sensation of vaginal tightness following radical cystectomy for vertical than for longitudinal retubularization. Of course the extent of disease influences the amount of upper vaginal wall that has to be removed, with possible significant limitations in size after reconstruction with both techniques.

Colorectal surgery

ED is a well-recognized complication of colorectal surgery and is usually a result of injury to pelvic autonomic nerves. The incidence after abdominoperineal excision or anterior resection for carcinoma is between 15% and 100%, whereas only 4.7% of men undergoing coloproctectomy for inflammatory bowel disease are affected. This difference reflects the more extensive resection required when dealing with malignancy: wide excision of perirectal tissues carries a greater risk of neural damage and consequent impotence than techniques such as close rectal dissection and mucosal proctectomy, which can be exploited in benign disease.

As in prostatectomy and cystectomy, accurate knowledge of the pelvic neuroanatomy is the key to preservation of potency. The pelvic parasympathetic nerves may be damaged at a number of points during rectal surgery. Excessive traction on the rectum during posterior mobilization can result in neuropraxia or avulsion of roots S2, S3, and S4.5 The pelvic plexus itself is most at risk during ligation of the middle hemorrhoidal vessels, to which it is intimately related. Neural injury may also occur during perineal dissection of the rectum. After division of the rectourethralis muscle, the neurovascular bundles are visible in association with the lateral prostatic fascia and are vulnerable to trauma by excessive dissection or diathermy anterolateral to the rectum. As stated, ED following colorectal surgery is usually neurogenic in origin. However, ligation of the anterior division or distal branches of the internal iliac artery is sometimes necessary. As a result, patients occasionally develop vasculogenic impotence, particularly if both internal pudendal arteries are ligated.

Vascular surgery

ED complicates between 30% and 80% of aortoiliac operations. Since pre-existing erectile problems due to atherosclerotic arterial disease or diabetes are also common in this population, sexual dysfunction is a major concern for some patients. The pelvic plexus and cavernous nerves are not at risk during dissection around the bifurcation of the aorta and iliac vessels. The internal iliac artery, however, is commonly occluded during these procedures, leading to a reduction in pelvic visceral blood flow and consequent vasculogenic ED.

Although restoration of adequate blood flow to the lower limbs or safe resection of aneurysmal disease are the primary aims in aortoiliac surgery, careful technique can allow preservation of potency in men with normal preoperative sexual function. Internal iliac ligation or embolization of atherosclerotic debris and thrombus into this vessel during flushing maneuvers should be avoided, if possible. It is also worth remembering that a number of patients with pre-existing vasculogenic impotence do regain erectile function following aortoiliac reconstruction. In one series, for example, sexual function was regained in 30% of patients with preoperative impotence and no normal patients were rendered impotent.

Treatment

Current treatment options for male ED are:

- the oral PDE-5 inhibitors sildenafil, vardenafil, and tadalafil;
- intracavernous injections of vasoactive agents [such as prostaglandin (PGE)-1];
- the vacuum pump; and
- different models of penile prosthesis that can be surgically implanted.
All these erectile aids are usually adopted after radical pelvic surgery with variable degrees of success depending on the patient’s motivation to resume sexual activity, treatment compliance, and the type of surgery (nerve-sparing versus non-nerve-sparing). As an example, the PDE-5 inhibitors, usually considered as the first-line treatment option, are thought to be highly ineffective after a non-nerve-sparing procedure since no amplification of the nitric oxide (NO) cascade occurs after the administration of a PDE-5 inhibitor in the absence of NO release from intact cavernosal nerve fibers. By contrast, the same drugs can produce a significant response rate when the nerves have been carefully preserved.

The same drugs have also been employed with a ‘prophylactic intent’ in order to optimize the recovery of spontaneous erectile function after a nerve-sparing procedure. Nocturnal penile tumescence is still severely impaired 8 months after a nerve-sparing radical prostatectomy as a consequence of neuropraxia of the cavernosal nerves.62 Early intake of a PDE-5 inhibitor at bedtime has been recommended with the aim of making nocturnal erections more potent. In the preliminary study by Padma-Nathan et al., patients who were potent preoperatively were randomized after nerve-sparing radical prostatectomy to sildenafil or a placebo for 36 weeks.63 Those who regained sexual function after 9 months of treatment (27%) also had better nocturnal erections recorded a year after the operation.

It is possible that sildenafil as well as the other currently available PDE-5 inhibitors may not be so effective in the early phase of nerve healing, as documented by the clinical inefficacy of sildenafil in the first 9 months after a nerve-sparing radical prostatectomy.64 Three-monthly intracavernous injections with PGE-1, starting the first postoperative month, significantly enhanced subsequent response to sildenafil compared with sildenafil alone started at the fourth postoperative month. At the 6 months’ follow-up, 82% of patients in the combination arm responded to subsequent sildenafil compared with only 52% in the sildenafil-only arm.65 Intracavernosal therapy has been found to produce a good erectile response in non-nerve-sparing patients and therefore it may be the treatment of choice in the early postoperative period following a nerve-sparing procedure. Similarly, the use of a vacuum constrictor device may facilitate early sexual intercourse and the potentially early return of natural erections, although no controlled study has been carried out to test this hypothesis.

Based on the few data available, either intracavernosal injections or a vacuum device should be offered as a first-line option for the first few months after the procedure, since their mechanism of action does not require intact neural tissue for erection. Thereafter sildenafil, or an equivalent PDE-5, may be a reasonable choice for those patients who can achieve at least a partial erection.

Conclusion

Recent advances in the understanding of pelvic autonomic neuroanatomy have led directly to the development of potency-preserving surgical techniques. These new approaches have had a major impact on surgical practice, particularly in urology. New approaches such as robotically assisted radical prostatectomy may result in improved potency outcomes as a result of improved visualization of the neurovascular bundles and a more proactive approach towards penile rehabilitation.66 As a result, it is now possible to preserve potency in many patients who undergo abdominal and pelvic surgery, without compromising cancer control.

REFERENCES


68. Chung MS, O’Connor RC, Laven BA, Orvieto MA, Brendler CB. Early release of the neurovascular bundles and optical loupes.


Rehabilitation of sexual function following prostatectomy

Francesco Montorsi and Alberto Briganti

Introduction

Radical prostatectomy is an increasingly used therapeutic option for patients with clinically localized prostate cancer and a life expectancy of at least 10 years. The pioneering work by Walsh and Donker significantly contributed to the understanding of the surgical anatomy of the prostate and posed the bases for the subsequent development of the anatomic radical prostatectomy technique (i.e., a surgical approach aimed at completely excising the prostate and providing optimal cancer control while maintaining the integrity of the anatomical structures devoted to the functions of urinary continence and sexual potency. Since the initial reports on this technique an increasing number of studies have reported very satisfactory postoperative rates of urinary continence, while the preservation of erectile function after surgery is clearly shown to be a major challenge for most urologists. This finding contributed to the development of an increasing interest in the elucidation of the pathophysiology of postoperative erectile dysfunction (ED) and its potential prophylaxis and treatment. Furthermore, ED after radical prostatectomy shows a profound effect on quality of life (QOL). Indeed it has been shown that more than 70% of patients who had undergone radical retropubic prostatectomy had a moderately or severely affected QOL because of their postoperative ED. Moreover, although the International Index of Erectile Function (IIEF) has been widely accepted as a validated instrument to assess ED, it has been demonstrated that different definitions of potency after surgery yield different results when applied to the same patients in the same time. This underlines the observation that sexual function entails more than penile erection (firm enough for intercourse) as the classic definition of potency.

Patient selection

The anatomical nerve-sparing approach to the prostate is considered for patients with clinically localized prostate cancer. A detailed description of the most widely used criteria to select patients eligible for a nerve-sparing procedure are detailed in Chapter 64. However, clinical stages T1 and T2 patients, as defined following digital rectal examination or transrectal ultrasonography of the prostate, are the best indicators. As clinical stage is often correlated to both prostate-specific antigen (PSA) levels and the biopsy Gleason sum, it has been suggested that a nerve-sparing approach may be considered in patients with PSA <10ng/ml and a Gleason sum ≤7.

Patients being considered for a nerve-sparing radical prostatectomy should be potent prior to the procedure. This is of major importance since patients who report some degree of ED or patients who use phosphodiesterase (PDE) type 5 inhibitors prior to the procedure are more likely to develop severe ED after the procedure itself. The use of validated questionnaires such as the IIEF may facilitate the diagnosis of preoperative ED during the initial patient assessment. This questionnaire assesses various domains of male sexuality, including erectile and ejaculatory function, orgasm, desire, and intercourse satisfaction, and the results of this patient self-assessment always yield useful baseline information. The morphology of the corpora cavernosa deteriorates with age and this may be correlated with the high prevalence of ED seen in aging men. Rates of recovery of erectile function after a nerve-sparing radical prostatectomy are inversely correlated with the patient’s age (i.e., the best postoperative potency rates are obtained in the younger patient population), and it seems reasonable to consider patients ≤55 years of age as candidates for a nerve-sparing procedure. Patient age also seems to be one of the most important factors for the recovery of sexual potency after unilateral nerve-sparing surgery. Indeed, in a group of 46 patients who received unilateral nerve-sparing radical retropubic prostatectomy, 14 (30.4%) regained full potency after surgery and, in the vast majority of them, recovery occurred within a period of 18 months. Of these patients, those aged <60 years reported the highest rate of recovery of potency sufficient for vaginal penetration after a mean of 13 months after surgery. Comorbid conditions also seem to affect the recovery of spontaneous erections postoperatively since they may have an impact on the baseline penile hemodynamics. A concomitant diagnosis of diabetes mellitus, hypertension, ischemic heart disease, or hypercholesterolemia or a history of cigarette smoking identified at the time of the preoperative patient assessment should be taken into account as a potential negative predictive factor for recovery of potency after surgery. Although a higher prostate volume could be associated with greater intraoperative bleeding, it does not seem to influence the postoperative potency rate. Nevertheless, body weight does not seem to be related to the feasibility of a nerve-sparing approach in patients who are clinically obese.
Surgical technique

In suitable candidates, radical excision of the prostate should be performed with the objective of achieving total cancer control (i.e., of removing all cancer present in the prostatic tissue) while maintaining the integrity of the anatomical structures on which urinary continence and erectile function are based. The corpora cavernosa receive the innervation responsible for erections through the cavernosal nerves, which branch out from the pelvic plexus. This latter structure is located adjacent to the tip of the seminal vesicles on the anterolateral wall of the rectum and may be damaged during radical prostatectomy. The cavernous nerves lie adjacent to small vessels forming the so-called neurovascular bundle along the posterolateral margin of the prostate bilaterally, and they are located between the visceral layer of the endopelvic fascia and the prostatic fascia. The neurovascular bundle is located at the 5 o’clock and the 7 o’clock positions at the level of the membranous urethra and, after piercing the urogenital diaphragm, it enters the corpora cavernosa, where it innervates the smooth muscle cells of the penile vessel walls and sinuses. It has been suggested that while the main trunk of the cavernous nerves runs posterolateral to the prostate from the level of the seminal vesicles to the prostatic apex, a significant number of nerves branch off the pelvic plexus to course along the anterolateral surface of the prostate. These nerves run between the prostatic fascia and the levator fascia. Distally, fibers of the cavernous nerves join together at the level of the urethral sphincter and are mainly located from the 4 o’clock to the 5 o’clock position and from the 7 o’clock to the 8 o’clock position. Based on the better understanding of the surgical anatomy of the prostate, Walsh and Garcia have clearly described the technique of anatomic radical prostatectomy in a step-by-step fashion.

The use of frontal xenon light and of magnifying loupes significantly improves vision during the procedure, and the authors of this chapter feel that this armamentarium should be always used when performing nerve-sparing radical prostatectomies. Indeed it has been recently demonstrated that the use of 2.5x optical loupe magnification during neurovascular bundle preservation was associated with a better recovery of erectile function after surgery, with a follow-up of more than 1 year.

Some crucial surgical steps deserve particular attention. Following pelvic lymphadenectomy, the endopelvic fascia is incised to allow the dissection of the prostatic apex. Care should be taken to ligate small branches of pudendal vessels located just underneath the endopelvic fascia in the area of the prostatic apex; cautery should not be used to secure these vessels in order to avoid damage to pudendal nerve branches also located there. Ligation of the Santorini’s plexus is a fundamental step in the procedure as it must guarantee perfect hemostasis in order to obtain the best visualization of the surgical field during the excision of the prostate. Walsh has suggested ligating the Santorini’s plexus distally first and subsequently dividing it with scissors; control of the proximal stump of the venous plexus is then achieved with a V-shaped suture, which avoids a central retraction of the neurovascular bundles, thus facilitating the nerve-sparing procedure. It has recently been suggested that control of Santorini’s plexus might be performed by using a small Allis clamp to grasp the two medial borders of the incised levator fascia. This maneuver is used to pull together only the superficial components of Santorini’s plexus; then, a 3–0 monocryl suture on a UR-6 needle is passed distal to the Allis clamp. It is important to note that this suture is not used to control all branches of Santorini’s plexus, since it is passed quite superficially to avoid any damage to the urethral sphincter. Indeed it allows the external urethral sphincter to be approached under direct vision, thus limiting the possible damage during its dissection. This passage is repeated twice and the suture is tied while leaving the Allis clamp in place. This maneuver allows the branches of Santorini’s plexus to be pulled together and facilitates its subsequent division. Santorini’s plexus is then sharply divided. A running suture with a 3–0 monocryl on a UR-6 needle is used to control bleeding from the deeper portion of the distal trunk of Santorini’s plexus. This suture must take only Santorini’s plexus; neither the urethral sphincter nor the most distal fibers of the levator ani (also named the levator urethrae) should be included in this suture, thus leaving the external sphincter and levator ani muscles completely intact. Once these bleeders are controlled, a running suture controlling the proximal (prostatic) trunk of Santorini’s plexus is used, following the technique described by Walsh.

After Santorini’s plexus has been controlled and divided the visceral layer of the endopelvic fascia should be bluntly incised on the lateral side of the prostate to allow for the gentle lateral displacement of the neurovascular bundles, which is obtained with the use of small sponge sticks. If this maneuver is performed correctly, the neurovascular bundles become clearly visible in most patients along their entire course from the membranous urethra and the seminal vesicles.

Other investigators have subsequently proposed different techniques aimed at achieving the best possible rates of postoperative normal urinary continence and potency, namely the importance of removing the prostate while leaving in place a large portion of the levator and prostatic fasciae that cover the gland has been recently proposed, by using both open and robotic techniques. A novel nerve-sparing surgical approach has been recently proposed, consisting of a high anterior incision of the levator and prostatic fascia aimed at efficiently preserving the urethral sphincter and neurovascular bundles during open radical retropubic prostatectomy. Indeed, starting from the bladder neck, using dissecting scissors the levator and prostatic fasciae are perforated and the development of the plane running between the prostatic capsule and the prostatic fascia is initiated. This plane is developed in a step-by-step fashion, from the region of the bladder neck to the urethral sphincter. The correct plane is easily identified because the reflection of the prostatic fascia is smooth and veins can be seen clearly, as through a transparent sheet. This maneuver must be performed very gently. In this way, the prostatic fascia is detached from the prostatic capsule and from the urethral sphincter. This maneuver allows for preservation of all vessels and nerves included between the prostatic and levator fasciae. The space created on both sides between the lateral border of the urethral sphincter, the prostatic apex, and the reflected prostatic fascia is usually remarkable in size. The dissection of the anterolateral surface of the prostate is extended as laterally as possible. When this
dissection is completed on both sides of the prostate, the urethral sphincter and the prostatic apex are clearly visible. By performing an incision of the levator fascia at the 1 o’clock and 11 o’clock positions to start the dissection of the neurovascular bundle, the largest possible fraction of the pelvic plexus branches, including cavernous nerve fibers, may be preserved.

Early release of neurovascular bundles laterally, starting from the apex of the prostate just after the division of the anterior urethra, has also been proposed and is associated with a greater percentage of patients reporting preserved erectile function after surgery than after a standard release of neurovascular bundles technique.29

It is mandatory to avoid the use of the cautery during every step of the prostatic excision. Recently, the Hopkins group has also suggested that any type of energy used during the dissection of the prostate will inevitably damage the neurovascular bundles: ultrafine clips and suture ligatures are thus recommended to guarantee adequate hemostasis during a nerve-sparing radical prostatectomy.29 As the pelvic plexus is located adjacent to the posterolateral tips of the seminal vesicles, particular care should be taken while excising them. The possible advantage of partial excision of the seminal vesicles to reduce the risk of damaging the pelvic plexus and thus preservation of postoperative urinary continence and erectile function has been reported.30 When pelvic hematomas occur it is advisable to drain them surgically since the fibrosis occurring after the slow spontaneous resolution of any blood collection significantly lengthens the duration of cavernosal neopraxia.

Although the number of cases performed per unit of time (surgeon’s volume) is a recognized predicting factor for success or failure in maintaining potency following a nerve-sparing radical prostatectomy, it has now been suggested that the surgeon himself probably plays the most fundamental role in determining the postoperative outcome: in other words, a large-volume surgeon may potentially keep doing things wrong if his surgical technique is not adequate.31 Therefore, an important take-home message is the need to compare one’s own surgical technique with that used by recognized experts in this field. Reviewing the videotapes of one’s own nerve-sparing radical prostatectomies and comparing the surgical technique and results seen in terms of margin status, urinary continence, and erectile function may be of significant importance because it allows identification of the parts of the operation that are at higher risks for surgical errors from a particular surgeon.32

Pathophysiology of erectile dysfunction following nerve-sparing radical prostatectomy

Patients undergoing nerve-sparing radical prostatectomy often experience impairment of erections in the early postoperative period. This has been related to the development of neuropraxia, which is believed to be caused by the damage to the cavernosal nerves that inevitably occurs during the excision of the prostate, even in the hands of most experienced surgeons. Absence of early postoperative erections is associated with poor corporeal oxygenation, which may facilitate the development of corporeal fibrosis, ultimately leading to veno-occlusive dysfunction.29

Recently, the role of apoptosis has been considered in the pathophysiology of post-prostatectomy ED. Apoptosis, or programmed cell death, is essential for the normal development of a multicellular organism as well as for physiological cell turnover. Morphologically this phenomenon is characterized by chromatin condensation, membrane blabbing, and cell volume loss. In the penis, chronic hypoxia and denervation have been shown to stimulate apoptosis: it is possible that cellular apoptosis leads to increased deposition of connective tissue that may finally lead to a decrease in penile distensibility.34-37 Recently, User et al. have elegantly elucidated the role of apoptosis in the pathophysiology of post-prostatectomy ED in a rat model.38 Post-pubertal rats were randomized to bilateral or unilateral cavernous nerve transection versus a sham operation. At different time intervals following the procedure, penile wet weight, DNA content, and protein content were measured. Tissue sections of the penis were stained for apoptosis and the apoptotic index was calculated. Finally, staining for endothelial and smooth muscle cells was done to identify the apoptotic cell line. Wet weight of the denervated penises was significantly decreased after bilateral cavernous neurotomy whilst unilateral cavernous neurotomy allowed much greater preservation of penile weight. DNA content was also significantly reduced in bilaterally denervated penises whilst no difference was found between unilaterally denervated penises and controls. Bilateral cavernous neurotomy induced significant apoptosis, which peaked on postoperative day 2. In addition, it was found that most apoptotic cells were located just beneath the tunica albuginea of the corpus cavernosum (i.e. the anatomical area where the subtunical venular plexus is located). Finally, these authors found that apoptotic cells were smooth muscle cells and not endothelial cells.

The subsequent hypothesis suggested by the authors was that the bilateral injury to the cavernous nerves may induce significant apoptosis of smooth muscle cells, particularly in the subtunical area, thus causing an abnormality of the veno-occlusive mechanism of the corpus cavernosum. Apoptosis also seems to play a role in the genesis of ED seen in the aging population (which is clearly of crucial importance in the radical prostatectomy patient group), since it has been shown that anti-apoptotic genes and proteins are expressed in young rats but not in aging rats.34

These findings on apoptosis following radical prostatectomy confirm the fact that most patients reporting postoperative ED do develop massive corporeal venous leaks in the long term.48 However, a reduction of the arterial inflow to the corpora cavernosa in patients with post-prostatectomy ED has been reported by several authors as a significant etiological cofactor.49,50 Postoperative penile hypoxia seems to play an important role in inducing histological and thus functional changes in the corpora cavernosa after surgery. Indeed, a recent clinical trial performed by Iacono et al. has clearly demonstrated that, in a selected preoperatively potent population of 19 non-diabetic patients undergoing radical prostatectomy and penile biopsies before surgery and at 2 months and 12 months after surgery, a progressive increase in penile
organized collagen content and a decrease in interstitial elastic fibers and smooth muscle cells was evident after surgery. The more relevant structural penile changes were reported at the 12-month follow-up biopsy evaluation. Interestingly, none of the preoperatively potent patients experienced return of spontaneous erections or responded to prophylactic postoperative sildenafil administration (100 mg, once weekly for 3 weeks starting 2 months after surgery), thus strongly suggesting that a non-nerve-sparing procedure had been performed in the same patients.

In conclusion, the postoperative combination of reduced penile arterial inflow and excessive venous outflow due to the apoptosis-induced damage of the veno-occlusive mechanism leads to reduced oxygen transport and increased production of transforming growth factor-beta. This subsequently causes significant tissue damage (i.e. increased corporeal fibrosis, which not only is at the root of the known penile hemodynamic abnormality but also is probably the cause of the postoperative decrease of penile length recently reported in an interesting study by Savoie et al.

Pharmacological prophylaxis and treatment of postoperative erectile dysfunction

Prophylaxis

The better understanding of the pathophysiology of post-prostatectomy ED, including the concept of tissue damage induced by poor corporeal oxygenation, paved the way for the application of pharmacological regimens aimed at improving early postoperative corporeal blood filling. Montorsi et al. showed that, by using intracorporeal injections of alprostadil early after a bilateral nerve-sparing radical prostatectomy, the rate of recovery of spontaneous erections was significantly higher than that in untreated patients. In the authors' experience, alprostadil injection therapy should be started as soon as possible after the procedure, usually at the end of the first postoperative month. The initial dose is alprostadil 5 μg. Patients should be instructed to use injections two or three times per week in order to obtain penile tumescence; injections are not necessarily associated with sexual intercourse but it is clear that if the patient desires, he may be able to resume satisfactory sexual intercourse with penetration as soon as he is able to identify the correct dosing of the drug. Brock et al. have also shown that the continuous use of intracavernous alprostadil injection therapy was able to bring about significant improvement in penile hemodynamics and a return of spontaneous erections (either partial or total) in patients with arteriogenic ED, thus confirming a potential curative role of this therapeutic modality in selected patients. These data have also been recently confirmed by Mulhall et al., who showed that the prophylactic use of intracorporeal injections of alprostadil in patients not responding to oral sildenafil resulted in higher rates of spontaneous functional erections and erectogenic drug response 18 months after nerve-sparing radical retropubic prostatectomy. The early postoperative use of intracavernosal injection therapy may also exert a significant psychological role. Commonly, after a nerve-sparing radical prostatectomy when the return of spontaneous erections is slow, a dysfunctional sexual dynamic may develop in couples. The patient withdraws sexually as he is increasingly discouraged with his lack of erectile function, which is a constant reminder of his cancer. The female partner is relieved that the patient has survived the surgery, and may be satisfied with his companionship and is anxious not to upset him by making sexual overtures that may frustrate him. Successful intracorporeal injection therapy early after radical prostatectomy may contribute to breaking this negative cycle.

Prophylactic administration of a vacuum constriction device has also been recently proposed as an early penile rehabilitation approach aimed at promoting adequate cavernosal oxygenation and therefore preventing penile fibrosis after surgery. The advent of PDE-5 inhibitors in the treatment of ED has clearly revolutionized the management of this medical condition. This class of agents acts within the smooth muscle cell by inhibiting the enzyme PDE-5, which naturally degrades cGMP, an intracellular nucleotide that acts as a second messenger in the process of smooth muscle cell relaxation. The cascade of intracellular events that leads to the relaxation of the smooth muscle cell is initiated by the release of nitric oxide, which follows sexual stimulation. Both intracorporeal cavernous nerve terminals and endothelium release nitric oxide, which as a gas diffuses into the smooth muscle cells and activates the enzyme guanylate cyclase, which ultimately catalyzes the reaction from guanosinetriphosphate to cGMP. Increased levels of cGMP lead to the activation of cGMP-specific protein kinases, which activate further intracellular events leading to the final reduction of intracellular calcium, this being associated with smooth muscle cell relaxation. At present, sildenafil, tadalafl, and vardenafil are approved for clinical use in the European Union and the USA and have been utilized also to treat post-prostatectomy ED.

The rationale for the use of these drugs as prophylaxis is not yet completely understood. However, recent studies have elucidated some potential mechanisms. The basic concept would be to administer a PDE-5 inhibitor at bedtime in order to facilitate the occurrence of nocturnal erections, which are believed to have a natural protective role on the baseline function of the corpora cavernosa. Montorsi et al. showed that when sildenafil 100 mg is administered at bedtime in patients with ED of various etiologies, the overall quality of nocturnal erections as recorded with the RigiScan device is significantly better than those obtained after the administration of placebo. Furthermore, experimental data regarding the potential mechanisms involved in chronic administration of sildenafil have been very recently published. Indeed, the effect of an 8-week treatment with sildenafil (60 mg/kg per day subcutaneously) in male rats was evaluated on electrically induced erectile response in vivo before and after an acute injection of sildenafil (0.3 mg/kg intravenously). Furthermore, endothelial-dependent and -independent relaxations of strips of corpus cavernosum were examined in vitro and compared with cavernosal strips from untreated rats. Interestingly, the authors found that endothelial relaxation induced by acetylcholine was significantly enhanced in rats treated chronically with sildenafil compared with untreated rats. This could imply
that either muscarinic receptors or the transduction mechanisms leading to the activation of endothelial nitric oxide synthase are up-regulated by chronic sildenafil treatment. Moreover, functional in vivo evaluations showed that chronic administration of sildenafil significantly enhanced frequency-dependent erectile response and was associated with a greater response to an acute injection of sildenafil in treated rats compared with controls. This study represents the first experimental support for chronic consumption of sildenafil, which could be associated with a higher rate of erectile function recovery after radical prostatectomy.

In this context, Padma Nathan et al. recently reported on the prospective administration of sildenafil 50 mg and 100 mg versus placebo, daily at bedtime, in patients undergoing bilateral nerve-sparing radical prostatectomy who were potent preoperatively. Four weeks after surgery patients were randomized to sildenafil or placebo for 36 weeks. Eight weeks after discontinuation of treatment erectile function was assessed with the question, ‘Over the past 4 weeks, have your erections been good enough for satisfactory sexual activity?’ and by IIEF and nocturnal penile tumescence assessments. Responders were defined as those having a combined score of ≥8 for IIEF questions 3 and 4 and a positive response to the above question. Twenty-seven percent of the patients receiving sildenafil were responders (i.e. demonstrated return of spontaneous normal erectile function) compared with 4% in the placebo group (p = 0.0156). Postoperative nocturnal penile tumescence assessments were supportive. We believe that in the hands of experienced surgeons a 27% overall rate of return to normal erectile function after a bilateral nerve-sparing procedure is far from being impressive, but the important message from this study is that daily bedtime administration of sildenafil 50 mg or 100 mg after this procedure should be able to improve every surgeon’s baseline results. Although similar data are not available yet for tadalafil and vardenafil, we believe there is no reason not to expect similar findings with these drugs.

Moreover, the rationale for PDE-5 inhibitor administration at bedtime in patients undergoing nerve-sparing radical retropubic prostatectomy has recently been evaluated by Bannowsky et al. In fact, in a cohort of 27 patients submitted to nerve-sparing radical retropubic prostatectomy, nocturnal penile tumescence recording during the acute phase after surgery showed residual erectile function as early as the first night after catheter removal. Conversely, in a small control group of four patients treated with non-nerve-sparing radical retropubic prostatectomy, no nocturnal erections were recorded early after catheter removal. Based on these results, the authors concluded that in cases of early nocturnal tumescence, administration of a PDE-5 inhibitor can support successful organ rehabilitation. However, further studies are needed to confirm the rationale of this approach.

Furthermore, early use of high-dose sildenafil after radical prostatectomy seems to be associated with preservation of smooth muscle content within human corpora cavernosa. Indeed, Schwartz et al. enrolled 40 potent patients affected by localized prostate cancer who underwent radical retropubic prostatectomy at a single institution and were subsequently treated either with daily sildenafil 50 mg (group 1) or 100 mg (group 2) for 6 months, starting from the day of catheter removal. Patients underwent percutaneous penile biopsy both preoperatively (under general anesthesia prior to surgical incision) and at 6 months after surgery (using local anesthesia). Interestingly, in group 1 there was no statistically significant change in the mean intracavernosal smooth muscle content between the preoperative and postoperative measurements (51.1% and 52.6%, respectively), but in group 2 a statistically significant increase in mean smooth muscle content after surgery (42.8% vs 56.8%, p < 0.05) was found. Thus, although it remains unclear how the chronic administration of sildenafil could increase the intracavernosal smooth muscle content after surgery, daily administration of high-dose PDE-5 inhibitors may be a key factor in cavernosal smooth muscle preservation, thus reinforcing the idea of the clinical application of sexual pharmacological prophylaxis after surgery.

However, despite the enthusiasm associated with these studies, the benefit induced by a rehabilitative PDE-5 inhibitor approach compared with an on-demand PDE-5 inhibitors schedule has not been confirmed. We recently prospectively studied a cohort of 80 patients submitted to bilateral nerve-sparing radical retropubic prostatectomy with adequate postoperative erectile function data 12 months after surgery. Patients were assigned to four different groups after surgery: no erectile therapy, on-demand intracavernosal injection of prostaglandin E-1 (PGE-1), on-demand PDE-5 inhibitors, and rehabilitative PDE-5 inhibitor therapy (either every day or every other day for 3 months). Interestingly, we did not record any significant difference 12 months after surgery in the mean IIEF erectile function domain score between patients who received PDE-5 inhibitors on demand and those treated with a rehabilitative intent. However, further large randomized trials are needed to confirm the validity of these preliminary data. Therefore, an open debate regarding the efficacy of an oral rehabilitation after radical prostatectomy is still ongoing.

Recently, a prophylactic regimen with methylprednisolone has been used in an interesting trial involving 70 young patients (40–60 years) undergoing bilateral nerve-sparing radical retropubic prostatectomy who were randomized to receive either 6 days of placebo or escalating doses of methylprednisolone starting from postoperative day 1. The rationale of corticosteroid use early after surgery was based on the potential use of this treatment in reducing the surgical neural inflammation and local edema that might contribute to postoperative dysfunction in neurovascular bundles. Nevertheless no clinical benefit has been reported in patients receiving corticosteroids compared with placebo in terms of erectile function recovery based on IIEF evaluation at the 3-month, 6-month, and 12-month evaluations (p = 0.08, p = 0.50, p = 0.71, respectively). Even in presence of disappointing results, many important factors such as timing of administration of the drug, doses used, and duration of therapy might be considered as potential explanation of lack of corticosteroid-induced benefits.

In practical terms, we feel that the need for postoperative prophylactic therapy should be discussed with the patient when counseling him about radical prostatectomy as one of the treatment options for prostate cancer. Patients must also have the chance to guide their choice by being informed of the
pharmacological approaches needed to recover normal postoperative erectile function.

**Treatment**

Phosphodiesterase type 5 inhibitors

PDE-5 inhibitors have acquired an established role in the treatment of post-prostatectomy ED. As the mechanism of action of this class of drugs implies the presence of nitric oxide within the corporal smooth muscle cells, only patients undergoing a nerve-sparing procedure should be expected to respond to these agents. Sildenafil is the drug that has been studied most extensively in this patient subgroup because it has been on the market worldwide since 1998. In general terms, it is now known that the best results with sildenafil are in young patients, those under 60 years of age being the best responders among patients treated having a bilateral nerve-sparing procedure. Sildenafil is usually administered at the largest available dose although it is common to have post prostatectomy patients responding also to the 25 mg and 50 mg doses. Typically the response to sildenafil has been shown to improve with time after the procedure: best results are seen from 12–24 months postoperatively.\(^5.55-62\) Unfortunately, no data from multicenter, randomized, placebo-controlled trials assessing sildenafil in patients undergoing nerve-sparing radical prostatectomy are available to date. It has been suggested that the early postoperative prophylactic administration of alprostadil injections allows a better response rate to subsequent sildenafil, with lower doses of the drug being necessary.\(^63\)

Several studies have been published regarding the postoperative benefit of sildenafil as treatment of ED after a nerve-sparing procedure.\(^55-59\) The response rate to sildenafil treatment for ED after radical prostatectomy ranged from 35% to 75% amongst those who underwent nerve-sparing surgery and from 0% to 15% amongst those who underwent non-nerve-sparing surgery. A recent report has identified many factors significantly associated with a successful outcome of sildenafil treatment after surgery in terms of erectile response, including the presence of at least one neurovascular bundle, a preoperative good erectile function [Sexual Health Inventory of Men (SHIM) score ≥15], age ≤65 years, and the interval from radical prostatectomy to drug use (more than 6 months).\(^64\)

Zagaja et al. found an inverse relationship between age and response to sildenafil therapy for ED after radical retropubic prostatectomy. Among men who underwent bilateral nerve-sparing surgery, response rates decreased from 80% in those <55 years to 45% in those aged 56–65 years and 33% in those >66 years.\(^65\) Zippe et al. stratified response rate by three time intervals post-surgery and by sildenafil dosage. The response rate increased with time during the first year: 3–6 months (44%), 6–12 months (55%), and <12 months (53%), and more responders required the 100 mg dose of sildenafil (71%) than the 50 mg dose (29%). Thus, the data suggest that the early initiation of treatment is recommended, but realistic improvement in response should not be expected until 1 year after surgery.\(^66\)

Raina et al. recently reported the long-term results of sildenafil use in patients affected by ED after radical prostatectomy.\(^67\) This study enrolled 91 patients stratified according to the type of nerve-sparing procedure they had undergone: bilateral nerve-sparing (53 patients), unilateral nerve-sparing (12 patients) and non-nerve-sparing (26 patients). All patients, at least 3 months after surgery, were prescribed sildenafil with the starting dose of 50 mg, which was titrated up to 100 mg in the case of non-satisfactory response. At the 12-month assessment performed by means of SHIM and Erectile Dysfunction Inventory for Treatment Satisfaction (EDITS) questionnaires, 48 of the 91 patients enrolled (52.7%) reported successful vaginal intercourse. This percentage increased up to 71.7% (38 of 53) if only those who had a bilateral nerve-sparing approach were considered. Moreover, at the 3-year follow-up assessment, 31 of 43 (72%) patients who returned the questionnaires were still using sildenafil for sexual intercourse, with a variable degree of partial erections. Interestingly, when the responses were stratified according to the neurovascular bundle status, the magnitude of improvement in SHIM score over time was greater in the bilateral nerve-sparing group than in the unilateral nerve-sparing and non-nerve-sparing groups. Significant erectile improvement was also reported by combining sildenafil 100 mg (taken 1 to 2 hours prior to intercourse) with vacuum tumescence device use in men affected by ED after radical prostatectomy who were dissatisfied with the results of the vacuum tumescence device alone.\(^68\)

Indeed, this combination regimen allowed for significant erectile improvement and sexual satisfaction in 77% of the patients (24 of 31); furthermore, the addition of sildenafil was associated with a significant increase in penile axial rigidity as reported by both patients and their partners. Moreover, 30% (7 of 24) of the patients responding to this combination treatment reported a return of natural erections at the 18-month follow-up.

Vardenafil has been tested in patients with ED following a unilateral or bilateral nerve-sparing prostatectomy in a multicenter, prospective, placebo-controlled, randomized study undertaken in the USA and Canada. This was a 12-week parallel arm study comparing placebo to vardenafil 10 mg and 20 mg.\(^69\) In this study patients in whom sildenafil had failed were excluded. Sixty percent and 71% of patients treated with a bilateral nerve-sparing procedure reported an improvement of erectile function following the administration of vardenafil 10 mg and 20 mg, respectively. A positive answer to SEF question 2 ("Were you able to insert your penis into your partner's vagina?") was seen in 47% and 48% of patients using vardenafil 10 mg and 20 mg, respectively. A positive answer to the more challenging SEF question 3 ("Did your erections last enough to have successful intercourse?") was seen in 37% and 34% of patients using vardenafil 10 mg and 20 mg, respectively.\(^70\)

Recently an extended analysis focusing on the other domains of the IIEF in the same patients undergoing nerve-sparing radical retropubic prostatectomy has underlined how vardenafil was significantly superior to placebo with respect to intercourse satisfaction, hardness of erection, orgasmic function, and overall satisfaction with sexual experience (\(p<0.0009\) vs placebo for each of the variables studied), both at 10 mg and 20 mg doses.\(^71\)

Tadalafil was also evaluated in a large multi-center trial conducted in Europe and the USA involving patients with ED following a bilateral nerve-sparing procedure. Seventy-one percent of patients treated with tadalafil 20 mg reported
improvement in their erectile function compared with 24% of those treated with placebo (p<0.001). The erectile function domain score of the IIEF was significantly higher after treatment with tadalafil 20mg compared with placebo (21.0 vs 15.2; p<0.001), and this difference was clinically significant.12 Tadalafil 20mg allowed men to achieve a 52% rate of successful intercourse attempts, which was significantly higher than the 26% obtained with a placebo (p<0.001).13

The adverse event profile of the three PDE-5 inhibitors has been very similar also in this patient population and the authors of this review feel that discontinuation from treatment with one of the PDE-5 inhibitors is usually caused by lack of efficacy and that tolerability is overall more than satisfactory.

Other medical treatments

Patients either not responding to or who cannot use PDE-5 inhibitors are typical candidates for second-line pharmacological treatment, which currently includes the intrarethral and the intracorporeal administration of alprostadil. The most recent information on the use of intrarethral alprostadil use suggests that its combination with oral sildenafil may salvage a significant proportion of sildenafil failures.69,70 Long-term efficacy and compliance data regarding intrarethral alprostadil as a treatment for post-prostatectomy ED showed that this therapy was effective in 55% of treated patients, with a drug compliance rate of 63% at mean follow-up of 2.3±1.2 years after surgery. Furthermore intrarethral alprostadil was associated with a significant increase in mean score on the SHIM compared with the preoperative period for all men enrolled and treated either with a nerve-sparing or non-nerve-sparing procedure. Better results in terms of treatment-induced erections were reported in patients with partially maintained erectile function after surgery (SHIM score ≥16).71

Intracorporeal injection therapy with alprostadil is effective in the majority of post-prostatectomy patients, regardless of the status of their cavernosal nerves. Recently, Gonzalez et al. have shown that the best clinical and hemodynamic responses with alprostadil injection therapy are seen 1 month after the procedure but that the attrition rate for this approach is higher when it is started at least 3 months after surgery. They proposed that in order to optimize long-term success with intracavernous injections of alprostadil, this treatment should be started 3 months after surgery, as a reasonable compromise between effectiveness and patient compliance.72

In the experience of the authors of this review, the use of alprostadil monotherapy should be matched against the use of the combination of alprostadil, papaverine, and phentolamine. Patients treated with the three-drug combination obtain very high response rates and only rarely report penile pain, the typical adverse event related to alprostadil.73 The major disadvantage of using the three-drug combination is its non-availability on the market, which obliges the urologist to prepare the solution and then distribute it to the patient.

This off-label use requires the approval of the Ethics Committee of the hospital and a signed informed consent from the patient. In a retrospective study conducted by Raina et al., 102 patients using intracorporeal injections for ED following radical prostatectomy were assessed by means of preoperative and postoperative SHIM questionnaire, a mean of 4.0±2.2 years after surgery.74 Of these 102 patients, 40 had a bilateral nerve-sparing procedure, 19 had a unilateral nerve-sparing procedure, and 43 had a non-nerve-sparing procedure. Injection therapy, based on the use of PGE-1 alone (10µg/ml or 20µg/ml in normal saline) (61% of patients), high-dose triple therapy (PGE-1 20µg/ml plus phentolamine 1µg/ml plus papaverine 30µg/ml) (19% of patients), or low-dose triple therapy (PGE-1 5.88µg/ml plus phentolamine 0.59µg/ml plus papaverine 17.65µg/ml) (20% of patients), was started a mean of 9 months (range 6–12) after the surgical procedure. Overall, 68% (69 of 102) of the patients achieved and maintained an erection sufficient for sexual intercourse and 48% (49 of 102) of the patients continued on long-term therapy. This excellent long-term efficacy, whatever the type of the intracavernosal compound used, has also been associated with a high compliance rate (<70% of the patients). Although no statistically significant differences have been reported among the three-drug formulation, no mention has been made by these authors regarding eventual differences in local or systemic side effects.

The same authors recently published an extended long-term analysis aimed at assessing the potential use of open-label sildenafil in men affected by post-prostatectomy ED, who had been treated for a mean of 3.7±1.9 years with intracavernosal agents, either PGE-1 alone or triple therapy (PGE-1 plus phentolamine plus papaverine). Overall, 41% of the patients enrolled (15 of 36%) successfully switched to sildenafil 50mg (27%) or 100mg (73%), with a higher switch rate obtained in previous PGE-1 users compared with patients using triple therapy, with a higher preoperative and post-intracavernosal injection SHIM score.75

Summary

Radical prostatectomy is an increasingly performed procedure in patients with prostate cancer. As the mean age of this patient group is progressively declining owing to the advent of prostate cancer screening programs, the demand for optimal postoperative QOL is becoming more important. Erectile function can be preserved in patients undergoing a nerve-sparing radical prostatectomy provided that patients are rigorously selected prior to surgery and that an anatomic radical prostatectomy following the most modern techniques is carefully performed. Pharmacological prophylaxis, either with oral or intracavernosal drugs, may potentially have a significantly important role in future strategies aimed at preserving postoperative erectile function.
REFERENCES


24. Walsh PC, Garcia JR. Radical retropubic prostatectomy: a detailed description of the surgical techniques. A video production of the James Buchanan Brady Urological Institute and Johns Hopkins Medical Video, a Division of Acceleara Inc. Available at http://urology.jhu.edu/


Sexual dysfunction and prostate cancer therapy

John M Fitzpatrick, Roger S Kirby, Robert J Krane, Jan Adolfsson, Don WW Newling, and Irwin Goldstein

Introduction

The management of prostate cancer focuses on effective methods of cure and palliation. The complications associated with radical surgery for localized disease, such as urinary incontinence and erectile dysfunction (ED), have been greatly reduced with the development of the nerve-sparing radical prostatectomy technique. In advanced disease, palliation of pain and prevention of additional complications of prostate cancer are the main treatment objectives. With the diagnosis of prostate cancer shifting to younger patients than was the case 10 years ago, and with the availability of effective treatment of localized disease, attention has shifted to issues of quality of life. Factors affecting patients’ lifestyles are being considered, sexuality in particular. Physicians should consider how a patient will feel when given treatment options that might deprive him of his sexual function. For all patients, seemingly irrespective of age, sexual dysfunction is still an important element in their perceived quality of life and must be discussed fully when planning any therapeutic strategy.

Causes of erectile dysfunction in prostate cancer

ED in prostate cancer patients has a number of causes (Table 66.1). Psychologically, some patients fear that sexual activity may cause pain, may stimulate the cancer, or, indeed, may cause the cancer to spread to their partner. Depression itself is an important cause of ED and loss of libido. Patients may also put up a psychological barrier to sexual activity because they feel less attractive to their partner. These issues must be taken into consideration when discussing sexual potency with prostate cancer patients. Pain from metastatic disease and lack of muscle strength are two important physical problems that can lead to ED. Painful gynecomastia may also limit sexual activity in some patients.

Treatment for prostate cancer can, in itself, cause a considerable degree of dysfunction (Table 66.2). Tissue fibrosis resulting in veno-occlusive ED can be caused in a variety of ways (Table 66.3). Absence of erections can lead to decreased blood flow to the corpora cavernosa. The concomitant reduction in oxygen supply to the tissues produces tissue fibrosis, which in turn leads to veno-occlusive dysfunction. The fibrosis is probably due to increased local deposition and activation of transforming growth factor beta-1, resulting from the ischemia.

Androgen withdrawal

Patients with advanced prostate cancer who are receiving androgen withdrawal therapy may be unable to develop erections and, in addition, may experience a loss of libido. Tiredness, reduced levels of concentration, and hot flushes are also serious side-effects, which may result in withdrawal from working life and an inability to enjoy hobbies. Androgen withdrawal can also produce a change in body image, with the development of a more female form; some men may fear the development of osteoporosis.

Radiation therapy

Radiation therapy (external beam), conformal beam radiotherapy, and brachytherapy can cause ED in 50%, 35%, and 25% of cases, respectively. Goldstein et al. evaluated radiation-induced alterations to penile hemodynamics using history, physical examination, and dynamic infusion phamacocavernosometry and cavernosography. The cause of ED was found to be arterial insufficiency, which has a higher incidence in smokers, older patients, and those with pre-existing vascular conditions, such as hypertension and diabetes.

Both proximal corporal veno-occlusive dysfunction and cavernosal arterial insufficiency were present in all patients. Cavernosography indicated that, in the majority of cases, site-specific venous leakage was crucial; proximal spongiosal, cavernosal, and dorsal venous leaks were far less frequent.

Surgery

Non-nerve-sparing radical prostatectomy can result in impotence rates as high as 98%. If preservation of the neurovascular bundles is achieved, the rate drops to between 30% and 75%, depending on whether the bundles are preserved bilaterally or unilaterally and on the patient’s age. ED following nerve-sparing prostatectomy may be due to removal of an accessory pudendal artery that had been acting as the main cavernosal artery. The prevalence of this phenomenon is
thought to be approximately 35%, with the origin of the artery occurring from the left side in 50% of cases and from the right side or bilaterally in 25% of cases each. In the majority of cases, the accessory pudendal artery arises from the internal pudendal or the obturator artery.

Management of erectile dysfunction

Normal sexual activity for a patient’s own age-group is an important consideration for urologists treating patients with prostate cancer. Older patients may be satisfied with less sexual activity and tolerate more complications than younger patients. Consequently, it is important to establish baseline values for sexual activity.

Patient expectations of treatment depend on a number of factors, such as age and disease stage. For instance, the expectations of a 40-year-old patient with localized disease who had full sexual function before therapy and is now left with no erectile function will certainly differ from those of a 75-year-old patient with metastatic cancer. Patient counseling is essential in order to clarify the likelihood of developing ED following treatment.

Patients should be made fully aware of the risk of dysfunction in order to avoid subsequent frustration, which in itself can lead to decreased potency. It is interesting to observe that, statistically, of the approximately 17 million men with ED of various etiologies in the USA, only 10% will seek treatment and even fewer will adjust to the subsequent therapy.

It is important to maintain sexual desire when treating patients with prostate cancer as, in most patients with an intact vascular system, loss of potency can be treated by injection therapy, vacuum pump devices, or a penile prosthesis. Loss of libido cannot be treated unless patients are given androgen replacement, and this is a separate but important issue. Injection therapy, if selected, should be started at an early stage, owing to the risk of tissue anoxia and corporal fibrosis associated with lack of erections. Injection therapy and vacuum devices appear to be acceptable therapeutic options from the patient’s perspective, although neither is without drawbacks. A penile prosthesis is another option that is sometimes requested at the same time as surgery for the cancer itself. Caution should be exercised in these circumstances, since it is not clear which patients will actually become impotent. The possibility of penile shortening following radical prostatectomy is a serious concern to patients. An assessment of penile length pre- and postoperatively in the erect state should be carried out to judge the effects of surgery accurately. The patient’s anger and frustration over this problem may be avoided with the use of a penile prosthesis at the time of radical prostatectomy.

Quality of life

Treatment choices for prostate cancer are frequently based on the evaluation of possible benefits balanced against side-effects of treatment. Owing to a lack of information, little regard is paid to quality-of-life issues.

Previous assessments of quality of life are unsatisfactory, because they measured sexual function and not how the patient felt about potency or lack of it. These assessments dealt only with figures, functions, and scales. Understandably, it may mean very little to the patient that he has a score of 10.7 on a ‘health and quality of life’ scale. Physicians should be aware that this assessment does not truly reflect the patient’s quality of life. For example, there are major differences between the patient’s and the physician’s appreciation of quality-of-life issues in endocrine treatment of prostate cancer.

Physicians tend to overestimate patients’ quality of life with respect to sexual activity and hot flushes, and underestimate their psychological distress. A validated instrument is essential in order for the physician to know what should be, and what is being, measured.

Quality-of-life instruments

A psychometric scale is the most commonly used method for evaluating quality of life. Each symptom experienced by the patient is given a value and the total score is analyzed statistically. Such symptom-based assessment can be carried out in a
number of ways: pain, fatigue, and general symptoms can be evaluated in a health-related quality-of-life questionnaire; alternatively, symptoms prevalent in a selected group of patients can be identified (e.g. characterization of symptoms related to localized or advanced prostate cancer) in order to evaluate sexual dysfunction.

Physicians need to devise methods of evaluating their patients’ symptoms in the absence of a validated questionnaire. The actual development of a formal questionnaire is a long and laborious process. Initially, in-depth interviews with a number of patients are conducted, followed by re-testing of the questions on a similar patient group. Validation should ideally be carried out against a ‘gold standard’ instrument of assessment, which unfortunately is not available in the area of sexual function. Test–re-test reliability is measured by asking the same question of the same group of patients after a specific time interval. It should be noted that the resulting questionnaire is specific only for the condition for which it was designed.

A questionnaire for assessing sexual function in patients with prostate cancer has been developed in Sweden by Helgason. A three-level approach was involved, with patients first being asked how frequently a particular dysfunction occurred; verbal categories of numbers (1–7) were used to represent the answers. The next question asked was: ‘If you were to live with this problem for the rest of your life, how much distress would you get from it?’ Four categories of answer were provided: none; a little; a moderate amount; and a lot. The third question, to which an answer on a scale of 1–7 was requested, was: ‘How would this affect your overall well-being, either psychological or physical?’ In this way, the questionnaire assessed three aspects of quality of life: function, inconvenience, and overall wellbeing, resulting in a scale specific to prostate cancer patients. Elements of the questionnaire were validated against objective measurements and found to have a very high reliability (90%). For example, three different aspects of erection were assessed with regard to nocturnal tumescence. The observation was made that all patients who said that they were impotent had no erections on the RigiScan device, compared with evidence of nocturnal tumescence in the 80% who said that they were potent.

The questionnaire was tested in men with and without prostate cancer, including 342 patients diagnosed in 1992 in Stockholm. An equivalent sample of healthy men from the general population was investigated. The assessment looked at the prevalence of decreased sexual function by comparing current function with that experienced in a patient’s youth. This also provided a ‘maximum’ function reference for each of the men studied.

One interesting observation was that there was a high prevalence of decreased desire and erections among the group of healthy men: 77% reported decreased function compared with that experienced in their youth (Table 66.4). The study indicated that the relative risk of experiencing ED and

<table>
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<th>Aspects assessed</th>
<th>Men without prostate cancer (n = 314)</th>
<th>Men with prostate cancer (n = 342)</th>
<th>Endocrine treatment/castration (n = 109)</th>
<th>Radical prostatectomy (n = 22)</th>
<th>External radiation (n = 37)</th>
<th>Mixed group (n = 35)</th>
<th>Other cases (n = 139)</th>
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<td>Sexual desire/ thoughts</td>
<td>156/305 (51%)</td>
<td>240/321 (75%)</td>
<td>82/99 (83%)</td>
<td>16/22 (73%)</td>
<td>27/37 (73%)</td>
<td>24/33 (73%)</td>
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<td>Erection capacity</td>
<td>235/304 (77%)</td>
<td>286/318 (90%)</td>
<td>93/97 (96%)</td>
<td>19/22 (86%)</td>
<td>35/37 (95%)</td>
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<td>Orgasm pleasure</td>
<td>209/305 (69%)</td>
<td>252/302 (83%)</td>
<td>81/93 (87%)</td>
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<td>78/89 (87%)</td>
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</tbody>
</table>

* Variations in denominators of ‘n’ are caused by different response rates for individual questions.

**Table 66.4** Proportion of men reporting decrease in sexual function compared with then youth; prostate cancer therapy indicated.

**Figure 66.1** Patient profile by treatment status.
a decreased sexual desire in prostate cancer patients in general was almost double that in the controls.

Patient preference survey

A survey was conducted in 400 patients with prostate cancer in four countries – the USA, Germany, Italy, and the UK. The objectives of the study were to investigate the patients’ understanding of the treatment options they received, to explore the importance of patient–doctor communication in the treatment of prostate cancer, and to determine the effect of treatment on patients’ sexual function. Concomitant conditions such as hypertension, heart disease, and psychological illness, therapy for which may have influenced erectile function, were not recorded. The majority of the patients were interviewed within 5 years of being diagnosed. Radical prostatectomy had been performed in 44.7% of patients, while 8.8% had received hormone therapy, and 3.5% had undergone bilateral orchiectomy (Figure 66.1). Patients were asked whether they were given sexual advice or help after diagnosis or treatment. Overall, of the five categories of healthcare professional about which enquiry was made, hospital doctors were cited as giving advice by 46% of patients, general practitioners by 21%, sex therapists by 9%, other professionals by 7%, and nurses by 3%. On a country basis, the hospital doctor was more likely to give advice in the USA, Germany, and Italy, whereas in the UK this advice was more likely to have been given by a sex therapist (Figure 66.2). With regard to patients who would find sex counseling helpful to themselves or their partner, 46% of all patients said that they would.

A comparison was made of patients’ sexual activity before diagnosis, 3 months after diagnosis, and in the previous month, and what the patient would prefer the activity to be (Figure 66.3). Clearly, patients in each of the countries studied would prefer their sexual activity to be the same as it was before diagnosis, or even greater. Patients’ preferences for the mode and frequency of delivery of hormonal treatment were studied, and interesting differences according to country were observed. In the UK, patients preferred to take one to three tablets daily, whereas in Italy, patients were more willing to have monthly injections (Figure 66.4). From a psychological viewpoint, seeing a patient on a monthly basis makes a significant difference.

The survey also showed a tendency for patients to discontinue certain hobbies and activities – an important aspect in terms of diminished quality of life. Almost one-third of patients gave up sporting activities, which (although this was not determined) could be because of pain or weakness caused by hormonal therapy.

In conclusion, this survey raised a number of important issues. Sexual dysfunction following therapy for prostate cancer should be assessed. Large multicenter, prospective, controlled studies into the incidence of ED after radical
prostatectomy are needed. With regard to hormonal therapy, the effect on sexuality should be assessed prospectively through questionnaires and objective methods. The problem must be quantified, with definition of the number of patients suffering from sexual dysfunction and the ways in which they are affected, and the effects on patient–partner relationships should be evaluated. Studies are also needed on what is considered to be the normal level of sexual activity in different age groups. In general, a universally accepted method of quantification of sexual dysfunction is urgently required, since this is an area that will be increasingly important to urologists involved in the management of prostate cancer.

REFERENCES

Introduction and history

Trans-sexualism is defined as ‘a strong and persistent cross-gender identification with persistent discomfort for the patient with his or her sex in the sense of inappropriateness in the gender role of that sex’. Until the late 1980s the prevailing assumption was that trans-sexualism was a well-defined identity with sharply marked boundaries. In the meantime it became evident that not all patients fit into these strict criteria. This may be the reason, that in the fourth edition of the Diagnostic and Statistical Manual (DSM-IV, published in 1994, the term ‘trans-sexualism’ is replaced by ‘gender identity disorder’. There are no specific laboratory or psychometric tests to confirm that a patient has an irreversible gender identity disorder.

The concept of medicalized sex change did not depend on the later invention of synthetic hormones or the development of elaborate surgical techniques. Ablative surgical procedures such as orchiectomy or hysterectomy have long been performed for sex change purposes before the term ‘trans-sexual’ was introduced into the scientific literature in 1923. It was in 1931 that a complete staged genital reassignment procedure in a male-to-female trans-sexual (MF-TS) was reported in a medical journal. In 1966 the influential book by Harry Benjamin, The Transsexual Phenomenon, brought genital sex reassignment surgery to a scientific level and made the medical societies aware of potential benefits of this type of surgery. It took another 14 years before the first standards of care were published in 1997, under the auspices of the Harry Benjamin International Gender Dysphoria Association (HBIGDA). These standards have been continuously updated, and the sixth version was published in 2001.1 Recently, the HBIGDA changed its name to the World Professional Association for Transgender Health (WPATH), and the latest standards of care for trans-sexual patients were published in 2001.3

These standards should be seen as an international interdisciplinary recommendation, which must be brought into context with national forensic and medical recommendations for the individual patient. Prevalence data for gender identity disorders vary with the survey methods used in various countries and have been reported as 1 in 2900 in Singapore and 1 in 36,000 in Germany. Gender identity disorders seem to affect more biological males than females with a sex ratio in various reports being about three males to every female.

The standards of care of WPATH reflect a professional consensus about the psychiatric, psychological, medical, and surgical management of patient with gender identity disorders. They provide minimum requirements for diagnostic and therapeutic procedures, consisting of:

- diagnostic assessment;
- real-life experience and psychotherapy;
- hormonal therapy; and
- surgical therapy.

Preconditions for surgical treatment in trans-sexual patients

If a patient has achieved 12 months of real-life experience (ideally combined with psychotherapy), received at least 6 months of continuous hormonal treatment, and has reached a reasonable understanding of the costs, length, likely complications and post-surgical rehabilitation requirements of the various surgical procedures, then readiness criteria for surgical treatment have to be approved and reconfirmed by two letters of recommendations from mental health professionals. The mental health professionals, the surgeon, and the patient share responsibility for the decision to make irreversible changes to the body. The two independent letters of recommendation by mental health professionals should be structured and clearly indicate surgical therapy.

The surgeon performing genital reconstruction should be a urologist, gynecologist, plastic surgeon, or general surgeon and be board-certified by a nationally known and reputable association. He or she should also have specialist competence in genital reconstructive techniques attained by documented supervised training, and be knowledgeable about more than one of the surgical techniques for genital reconstruction.

Genital surgery for the MF-TS patient can include orchiectomy, penectomy, vaginoplasty, clitoroplasty, and labioplasty. Techniques include penile skin inversion and pediced rectosigmoid transplant of free skin graft to line up the neovagina.

Genital surgery for the female-to-male trans-sexual (FM-TS) patient can include hysterectomy, salpingo-oophorectomy, vaginectomy, metoidioplasty, scrotalplasty, urethralplasty, placement of testicular prosthesis, and phalloplasty. There are various current operative techniques for phalloplasty. Even metoidioplasty, which in theory is a one-stage procedure for construction of a microphallus, often requires more than one operation. The plethora of techniques for penis reconstruction indicates that further technical development is necessary.3
Surgical reassignment in male-to-female trans-sexuals

Non-genital surgery

Even after several years of estrogen therapy, breast formation is often insufficient and requires operative breast augmentation. Despite some sexual differences in mammary anatomy, and chest wall anatomy, the implantation of mammary prostheses is not essentially different from a breast augmentation in biologically female patients. Further operative procedures such as cricothyroplasty for voice augmentation or resection of the thyroid prominence as well as rhinoplasty to provide the patient with a more feminine nose profile may be indicated.\(^4\) Timing of all these procedures in relationship to surgical genital reassignment is optional. It may be prudent to postpone breast augmentation for several months after genital reassignment in order to await the potential effect of castration on breast tissue. If breast surgery is performed together with genital surgery, it should be the first step of the procedure since it represents the most aseptic part of the intervention.

Genital reassignment surgery

The goals of genital gender reassignment surgery in MF-TS patients summarized by Karim et al. in 1996: three “The surgical aim of genital reassignment in MF-TS is to create a perinegenital complex as feminine in appearance and function as possible. The perineogenital area should be free of poorly healed areas, scars and neuromas. The neovagina should ideally be lined with moist, elastic and hairless epithelium. Its depth should be at least 10cm and its diameter should be 30mm’ (Table 67.1).

Vaginoplasty

Methods for the lining of the neovaginal cavity between both sheets of Denauvielle’s fascia can be classified into five options:5

1. Non-genital skin grafts
2. Penile skin graft
3. Penile scrotal skin flaps
4. Non-genital skin flap
5. Pedicled intestinal transplants.

While non-genital skin grafts were used in the first reports on genital reassignments,\(^7\) disadvantages such as donor area scars, frequent circular scar formation at the introitus, suboptimal sensation, and lack of any lubrication have withdrawn attention from these techniques as first-line procedures. Penile skin grafts were popularized in the early period of genital reassignment and represented some advantages over non-genital skin, but consensus developed in the past few decades that conversion of a possible skin flap into a graft does not seem to be justified.\(^8\) Non-genital skin flaps, such as medial thigh flaps or inguinopudendal flaps, have been reported but have never gained widespread popularity owing to the resulting donor site morbidity and the bulky flap characteristics, which may reduce neovaginal volume. These techniques may be more appropriate for genital reconstruction in biologically female patients after cancer surgery.

Pedicled intestinal transplants have been used in transsexual patients since 1974. A similar appearance to normal vaginas and lubrication may be possible advantages; nevertheless, this approach demands additional transabdominal surgery with all its possible inherent complications. Retention of mucus, introital stenosis, persistent odor, and colitis are further possible complications, which make these techniques less attractive as a primary procedure.\(^4\) Rectosigmoid transplants remain a viable option for secondary vaginoplasties after failed penoscrotal flap procedures or in non-trans-sexual women with vaginal atresia.\(^6\)

Penoscrotal skin flaps today are favored by most authors in the field of trans-sexual surgery. The inverted penile skin is used as a tube, augmented by a triangular perineal–scrotal flap for construction of the posterior introitus (Figure 67.1).

Several modifications have recently been published – for example, the inclusion of a pedicled and opened urethral segment into the tube for diameter enlargement and better lubrication.\(^9\) In patients with a short penis or a radical circumcision, the length of the inverted penile skin may be too short to reach the neovaginal vault. In these cases elongation of the penile skin tube may be facilitated by split skin grafts or full scrotal skin grafts after thinning and depilation.\(^10\)

Daily postoperative dilatation of the neovagina is of utmost importance for preservation of neovaginal length and width. Several obturators have been recommended for this purpose. A pneumatic soft silicone device with a valve for individual filling may be an attractive dilator for the first 6–8 weeks after surgery. This should be replaced by a more solid device after wound healing in order to prevent contractile scar formation. Patients must be informed that vaginoplasty with skin lining demands lifelong regular self-dilatation, which only rarely can be replaced by sexual intercourse. Shrinkage of the neovaginal cavity with need for secondary procedures occurs in less than 10% of cases in large-volume centers that specialize in

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Table 67.1 Steps of genital sex reassignment surgery in male-to-female trans-sexual patients

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<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Bilateral ablation of the testes</td>
</tr>
<tr>
<td>2.</td>
<td>Amputation of the penis</td>
</tr>
<tr>
<td>3.</td>
<td>Creation of a neovaginal cavity with a sensitive lining</td>
</tr>
<tr>
<td>4.</td>
<td>Creation of a female urethral meatus</td>
</tr>
<tr>
<td>5.</td>
<td>Construction of labia and clitoris</td>
</tr>
</tbody>
</table>

sex-reassignment surgery. If the penile skin is not sufficiently long to reach the neovaginal wall, extensive infra- and supra-pubic mobilization of the penile island flap is demanded. There is no supporting evidence in the literature to recommend whether the neovaginal lining should be fixated to the sacrospinous ligament or to the rectus muscle.

Clitoral–labioplasty

The creation of a sensitive, well-vascularized neoclitoris during MF-TS genital reassignment has been accepted as a very important surgical step. Up to 1995 it was not an integral part of surgical standards in reassignment surgery. Since then nearly all reports on MF-TS genital reassignment include clitoroplasty in the standard surgical procedure: part of the glans penis, with the neurovascular dorsal bundle in continuity, is dissected from the corpora cavernosa for this purpose. Torsion- and pressure-free positioning of the bundle is essential in order to avoid postoperative necrosis of the neoclitoris. More than 80% of operated MF-TS patients report erogenous sensation of the neoclitoris after this procedure. Complete resection of both corpora cavernosa and partial resection of the corpus spongiosum are further important steps to refine the vestibulum and introitus area in order to avoid obstruction during intercourse caused by arousal-induced swelling of erectile tissue.

The creation of esthetically acceptable labia majora from scrotal skin normally does not represent a problem for surgeons experienced in gender reassignment surgery. In the majority of cases, sufficient well-vascularized scrotal skin is available for labia formation. Creation of an esthetically appealing posterior commissure is facilitated by a small posterior base of the inverted Y-incision, advocated by Karim et al. in 1995.

Strong tension on the abdominal pedicle of the penile skin flap used for inversion vaginoplasty results in the ventral aspect of the labia majora remaining too far apart. In order to correct this anterior dehiscence of the labia majora simultaneous infrapubic double Z-plasties have been recommended. These additional incisions may endanger penile skin blood supply and result in hypertrophic scar formation, owing to high tension on the suture lines. Consequently, it appears wise to delay these procedures until complete wound healing has occurred. Recently, much effort has been invested by several surgical teams in sophisticated techniques for reconstruction of the clitoral–vestibular–labial complex during primary genital reassignment procedures. It remains open to debate whether such detailed procedures might be better performed as planned secondary procedures after complete wound healing.

Postoperative follow-up studies

A comprehensive compilation of follow-up studies after gender reassignment surgery was published by Pfäfflin et al. in 1992. An actual analysis of this and other compilation reports by Hartmann et al. identified a negative postoperative outcome in about 15% of all operated patients. Good surgical results have been identified as a significant indicator for overall positive outcome. Advanced age at first presentation and personal as well as social instability have been identified as negative predictors. Considering the progress of surgical techniques achieved in the past 15 years, it may be wise to search for follow-up studies comparing older and newer operative strategies. Van Eldt et al. examined 93 MF-TS patients after surgery and were able to compare results before and after 1996. Hospital stay and the number of re-admissions and re-operations significantly dropped after changing to newer
operative strategies. Stenoses of the neovagina were common after split skin graft lining, but 32 of 42 patients were content with vaginal volume after the introduction of the use of peno-scrotal skin for neovaginal lining. Over 80% stated satisfaction with their status after surgery. From other reports it becomes obvious that satisfaction with vaginal volume can be observed in around 74% of all operated patients. A 10–20% stenosis rate has to be expected after vaginoplasty.\textsuperscript{10-13} If the neurovascular bundle is preserved, an 80–87% clitoral orgasm rate can be achieved.\textsuperscript{10,13} A re-operation rate of more than 20% has to be expected, mostly because of a need for corrective surgery to the introitus and the clitoral labial complex.\textsuperscript{3}

Surgical reassignment in female-to-male trans-sexual patients

Breast reduction

Obtaining a male chest configuration is of utmost importance for FM-TS patients. A subcutaneous mastectomy in patients with larger breasts is a significantly more difficult operation than simple breast augmentations in MF-TS patients. It should precede other operative procedures, and it greatly facilitates the real-life test and the adjustment to a male lifestyle. In the case of small breasts and elastic skin, a simple semi-areolar incision can be used for subcutaneous mastectomy. In patients with larger breasts, skin reduction is required and usually performed by circular periareolar excision and de-epithelialization.\textsuperscript{4}

Hysterectomy and oophorectomy

Hysterectomy and oophorectomy may be performed as a preliminary procedure to reconstructive genital reassignment in FM-TS patients, or it may be an integrated part of the procedure. ‘All-in-one’ procedures may be more cost- and time-effective, but they expose the patient to extended trauma, blood loss, and anesthesia time. The actual standards of care available do not permit a conclusion to be drawn as to which of the options may be recommended.\textsuperscript{3,4,13,22} If hysterectomy and oophorectomy are performed as a separate first step of gender reassignment, vaginal length should be reduced as much as possible during the hysterectomy in order to facilitate later colposcisis. The gynecologists performing these procedures should take care to prevent damage to abdominal wall blood vessels during the hysterectomy, which may be important as future recipient vessels during free-flap transposition for penile reconstruction (the inferior epigastric artery and vein).

Metoidioioplasty

The first description of surgical enlargement procedures using the clitoris, date back to 1973. The techniques have been subsequently refined and have come to be called ‘metoidioioplasty’ or ‘metaidioioplasty’.\textsuperscript{23} Long-term androgen treatment in FM-TS patients stimulates the growth of the clitoris, in some patients to a degree where this organ can serve as a penis. Actual techniques include release of the ventral clitoral chorda and ligaments with consequent strengthening and lengthening of the clitoris. A urethroplasty to the tip of the clitoris is performed using vestibulum and labia minora. An anterior-based vaginal flap can be included in the urethroplasty, the rest of the vagina is completely excised, and the labia majora reconstructed into a neoscrotum.\textsuperscript{24} Recently Hage and Van Turnhout analyzed the long-term results of such a procedure in 70 patients.\textsuperscript{25} An average of 2.6 surgical procedures per patient was needed to complete genital reassignment and manage such postoperative complications as urinary fistulae and stenoses. In 17 of the 70 patients, additional phalloplasty with free flaps was performed after metoidioioplasty. Metoidioioplasty may be the method of choice in FM-TS patients who are in doubt about their need for phalloplasty, but patients should be informed that complication rates and the need for re-operations are considerable. Owing to the recent advances in free-flap phalloplasty these procedures will become less attractive for FM-TS patients in the future.

Phalloplasty and scrotal reconstruction

The first series of successful phalloplasties, using a tubed abdominal flap, was reported by Bogoras in 1936.\textsuperscript{26} During the following decades the search for the best method encompassed numerous variations of abdominal flaps, scrotal skin flaps, tubed thigh flaps, gracilis musculocutaneous flaps, groin flaps, and iliac crest flaps. In 1984 the first neophallus derived from microsurgically transplanted free radial forearm flaps initiated a plethora of free-flap designs and techniques. The availability of microsurgical neurovascular anastomoses enabled reconstructive surgeons to look for other less exposed donor areas for free-flap retrieval, such as upper medial arm, upper lateral arm, and saphenous, deltoid, and fibular osteocutaneous flaps.\textsuperscript{27} The variety of more than 20 different free and pedicled flaps that are used for phalloplasty suggests that one single ideal technique that fulfills all the demands of neophallus formation does not exist (Table 67.2).\textsuperscript{28}

The most promising techniques are described below, with an emphasis on recent reports by interdisciplinary teams from peer-reviewed journals. To date, no detailed standards of care concerning operative techniques exist.

Regional flaps for phalloplasty

Before microsurgically transplanted free flaps were introduced, regional flaps represented the only possibility of adequate

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<th>Table 67.2 Goals of modern phalloplasty</th>
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<tr>
<td>A one-stage procedure that can be predictably reproduced</td>
</tr>
<tr>
<td>Creation of a competent neourethra to allow for voiding in the standing position</td>
</tr>
<tr>
<td>Return of tactile and erogenous sensibility</td>
</tr>
<tr>
<td>Enough bulk to tolerate the insertion of a prosthetic device</td>
</tr>
<tr>
<td>A result that is esthetically acceptable to the patient</td>
</tr>
<tr>
<td>Minimal scarring or disfigurement</td>
</tr>
<tr>
<td>No functional loss in the donor area</td>
</tr>
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</table>

From Semin Urol 1987; 5: 262–69.\textsuperscript{26}
tissue transfer for neophallus reconstruction. They still remain a viable option in many centers specializing in reconstructive surgery. Bettocchi et al. compiled long-term follow-up data from 85 FM-TS patients after pedicled pubic phalloplasty, including urethroplasty to the tip of the neophallus. The stricture and fistula rate was 94%, so that after 1993 the team switched to a two-stage procedure in order to reduce urethral complications. However, more than 50% of these patients developed urethral complications.29 If prosthesis implantation was desired, malleable devices tended to erode distally (50%) which could be overcome by implantation of hydraulic devices within a Dacron® sleeve as a tunica albuginea substitute. In the authors’ institution, a bilateral groin flap technique, including a unilateral rectus muscle flap, has been in use since 1988.30 The bulk of rectus muscle permits simultaneous implantation of a malleable or hydraulic prosthetic device without significant risk of erosion. The proximal urethra is reconstructed from vestibulum and labia minora up to the clitoral tip. The clitoris remains in place due to the low sensitivity of pediced regional flaps. A second operation is generally necessary for scrotal reconstruction by VY-plasty of the labia majora and for thinning of the bulky neophallus.

An analysis of 136 cases of phalloplasties using various methods of local flaps and distant free flaps compared favorably for local flaps with regard to postoperative shrinkage and necrotic complications as well as the size of donor site defects.31 It must be noted that procedures using distant free flaps were accompanied by an unacceptably high complication rate in this series.32

Free flaps for phalloplasty

Recent publications on the use of free flaps for phalloplasty concentrate on the fibula and forearm as preferred donor sites. In 1993, Sadove et al. popularized fibula flaps for penile reconstruction as so-called free sensate osteocutaneous fibula flaps.33 Part of the fibula was included as a substitute for penile stiffening. The urethra reconstruction was first accomplished by full-thickness skin graft and later by ‘pre-fabrication’ several months before flap transfer. Split skin or full-thickness skin was rolled over a 22–30F catheter and inserted at the desired length into a subcutaneous tunnel of the flap area.34 The operation included coaptation of lateral sural nerves to adequate cutaneous nerves deriving from the ilioinguinalis nerves or iliohypogastricus nerves. The use of dorsal clitoral nerves for coaptation to flap nerves was successfully attempted.35 Preferred recipient vessels were the femoral artery and branches of the long saphenous vein. Flap size depended on anatomical preconditions and was about 20cm in length and 12cm in width.

During the past 5 years it has become obvious that phalloplasty from fibula free flaps is best accomplished as staged procedures. Proximal urethroplasty to the tip of the clitoris is combined ideally with vaginectomy and should precede fibula flap transfer by several months.33 Fibula bone inclusion in the flap is still a point of debate and many plastic and reconstructive surgeons prefer vascularized bone segments to synthetic prosthetic material. Nevertheless, a permanently rigid structure in the neophallus has to be considered as an imperfect solution. The most important shortcoming may be the resulting donor site morbidity with the need for wearing a lower leg splint for at least 6 weeks and the potential for long-term donor site problems with decreased power, suboptimal gait co-ordination, and ankle instability. A recent report on the use of a septocutaneous fibula free flap without fibula bone may help to modify the technique and to decrease morbidity.35

In experienced hands, the free forearm flap has gained increasing acceptance over the 23 years since its first description. It has also been used as an osteocutaneous flap, but significant donor forearm morbidity in half of the patients made this modification less attractive.36 In specialized centers, where urologists and plastic reconstructive surgeons work together, the free forearm flap without urethral pre-lamination and without inclusion of osseous segments has become the first choice for penile reconstruction.4,29,31,33,35 Functionally and cosmetically, microsurgical free forearm flaps lead to the best results.39 Furthermore the operation may be done as a one-session procedure by an interdisciplinary team (Table 67.3, Figures 67.2 and 67.3).

Details of the operation may differ between leading centers in this field. Some authors prefer to select branches of the ilioinguinalis or iliohypogastricus nerves, others prefer clitoral nerves for coaptation of the forearm nerves. The clitoris is usually denuded and buried underneath the neophallus.3

Owing to the complexity of the operation, complications are numerous and should be explained in detail to the patient. These include:4,41

- partial or total flap loss, occurring in less than 5% of cases;
- nerve compression or compartment syndrome, owing to the prolonged lithotomy position, occurring in less than 2% of cases; and
- urethral complications, such as fistula formation or stenoses, the leading causes of re-intervention, occurring in around 50–60% of cases.

Penile prosthesis implantation after phalloplasty

Implantation of testicle and penile prostheses can be undertaken 6–12 months after complete urethral healing and after

<table>
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<th>Table 67.3 Steps in one-session genital realignment in female-to-male trans-sexual patients using the free forearm flap</th>
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</thead>
<tbody>
<tr>
<td>1. Hysterectomy, oophorectomy, vaginectomy (gynecologist)</td>
</tr>
<tr>
<td>2. Proximal urethroplasty, colpopexis (urologist)</td>
</tr>
<tr>
<td>3. Preparation of recipient nerves and vessels (urologist)</td>
</tr>
<tr>
<td>4. Scrotoplasty (urologist)</td>
</tr>
<tr>
<td>5. Retrieval of full skin graft from the groin (urologist)</td>
</tr>
<tr>
<td>6. Free forearm flap, including distal neourethra by tube-in-a-tube formation (plastic surgeon)</td>
</tr>
<tr>
<td>7. Free flap transfer and microsurgical nerve and vessel coaptation (plastic surgeon)</td>
</tr>
<tr>
<td>8. Urethral anastomosis (urologist)</td>
</tr>
<tr>
<td>9. Full skin graft coverage of forearm defect and primary closure of the harvesting site in the groin (plastic surgeon)</td>
</tr>
</tbody>
</table>

From World J Urol 1987; 5: 9–13.41
return of tactile sensitivity to the neopenis. The best functional and esthetic results are obtained by using hydraulic multicomponent devices, including a covering of the cylinders with Dacron® in order to prevent migration and erosion of the device. The Dacron® sock should be fixed to the lower arch of the pubic bone with non-resorbable sutures. In the authors’ experience, prosthesis implantation should be done in two sessions: during the first session one hydraulic cylinder is implanted with a Dacron® sock and left in half-inflation. During the same session two testicular prostheses are implanted into the neoscrotum formed from the labia majora. After 3 months a reservoir is positioned beside the bladder and one testicular prosthesis is replaced by the prosthetic pump mechanism. Pre-formation of the scrotal cavity lined by a fibrous capsule caused by the temporary implantation of a testicular prosthesis enables subsequent easy handling of the pump mechanism by the patient. Nevertheless, complications are expected to be more frequent than after penile prosthesis implantation in biologically male patients (10–20%) and should be explained in detail to the patient (see Figure 67.3). In a comprehensive follow-up report by Eldn et al. in 1997, more than 80% of patients stated an overall satisfaction with their new postoperative situation after regional flap phalloplasty. Hoebbeke et al. reported a successful prosthetic implantation in 32 of 35 FM-TS patients after complete forearm flap penile reconstruction; of these, 29 were sexually active with a partner and reported patient satisfaction.

In the authors’ institution, 140 FM-TS patients had a complete penile reconstruction by forearm flaps between 1990 and 2007. Preliminary data from 29 patients who recently underwent subjective and objective follow-up showed that 70% were able to have sexual intercourse, 72% were able to reach orgasm by neophallus stimulation, 90% were able to void in a standing position, and 90% would undergo the procedure again if necessary. Measurement of pudendus sensory evoked potentials showed normal or slightly prolonged latency times in 27 patients. In all these patients at least one clitoral nerve had been coapted to the forearm flap nerves under microsurgical conditions, which may prove the possible efficiency of this technique to give erotic sensitivity to a neophallus.

Conclusive long-term follow-up data on the wide variety of newer surgical techniques for neophallus reconstruction is still lacking. However, microsurgically transferred free forearm flap, followed by later implantation of a hydraulic three-component prosthetic device, seems to be the most promising approach.

Postoperative follow-up studies

Follow-up studies published before 1991 are not helpful owing to the lack of modern phalloplasty techniques at that time.
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